BRAIN.

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THE OCCURRENCE OF UNSUSPECTED INVOLVEMENT OF THE CENTRAL NERVOUS SYSTEM IN UNSELECTED CASES OF SYPHILIS.

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I.—Introduction.

During recent years great interest has developed in the study of syphilis as it affects the central nervous system in the early stages of the disease.

It has been realized gradually that "gummatous meningitis," which a few years ago was the only recognized form of syphilitic brain disease, other than dementia paralytica, is an incorrect term if it implies that the lesion is a tertiary phenomenon only.

It became quite common to find this condition in the later secondary stages and then earlier in the secondary stage. Next, cases of "secondary syphilitic meningitis" were quoted which could not be accurately described as "gummatous" at all.

With increasing investigation of early cases of syphilis by neurologists, it began to be suspected that affections of the nervous system were really not uncommon in such patients, although they did not necessarily lead to pronounced symptoms.

Evidence then began to accumulate that such affections as were clinically detectable were in reality only a fraction of those which really existed; that the nervous system was frequently attacked without any outward indication of this being manifest.

The origin of this further advance may be taken to be a series of papers by Ravaut (1903) [19]. This author performed the operation of lumbar puncture upon a number of secondary syphilitics, most of whom showed no evidence of nervous disease, and in a large proportion found a pleocytosis and other pathological changes to be present in the cerebrospinal fluid. For instance, in 100 cases of early secondary syphilis there were only twenty-eight which could be said to have quite normal cerebrospinal fluids.

After this observation no further contribution was made to this subject for several years.

About the year 1911 a discussion arose as to the effect of "606"

treatment upon the central nervous system. It was asserted by one school, and especially by Finger, that "606" actually induced a toxic reaction in the central nervous system which was recognized by an increased number of nervous signs following the treatment.

The nature of this toxic reaction was not at first clear. Some considered it to be a direct arsenical intoxication such as was known to occur (optic atrophy) after the administration of arsenic, while others considered that the lesion was syphilitic. This latter view soon became general (*vide* McIntosh and Fildes, 1911 [16]), and then the question arose as to whether these syphilitic affections of the central nervous system were commoner after "606" than after mercury. An extensive literature appeared upon this subject of the "nerve relapse." Ehrlich and his school argued that such relapses were quite common in the literature of mercury treatment (Benario). Without entering into all details it may be said that at the present time it is accepted that this was the case and that nervous affections are not unduly common after "606." On the other hand it is also accepted that such manifestations are remarkably common not only after "606" but before "606" or any other treatment has been administered.

The recognition of these "nerve relapses" and the consequent discussion greatly stimulated the neurological examination of cases of syphilis. Small signs were recognized which were formerly missed and the operation of lumbar puncture became a routine in neurological clinics. It was however only the cases which exhibited nervous signs which came into the hands of the neurologist, and thus it only gradually became evident that changes might be present in the cerebrospinal fluid when no obvious nervous lesion existed, as had been shown already by Ravaut.

These observations are sparse and often trivial.

In 1911 Boas and Lind [4] examined six cases of untreated secondary syphilis and found a slight increase in cells in two. Fraenkel [11] in 1912, in fifteen cases of syphilis described without detail, but including some late secondary cases, found five with increased cells and positive Wassermann reactions in the fluid. Whether the five cases on careful examination would have presented signs of nervous disease is not clear. The remarks upon the nervous system are confined to the letters "O.B."

Zalozieoki and Frühwald [24] in the same year examined thirty cases of early but unspecified syphilis without evidence of nervous disease. Four of these had an increase of cells in the cerebrospinal fluid (11 to 24 per cubic millimetre), five had 22 to 87 cells and also

increased globulin, while two had 94 and 212 cells, increased globulin and positive Wassermann reactions. One of these was a late case of secondary syphilis (infection two years), and ophthalmological examination revealed a "pseudoneuritis." Otherwise the nervous systems of both were normal.

Bergl and Klausner (1912) [5] examined twenty-six cases. Four of these were suffering from primary syphilis and two had eight cells per cubic millimetre. The remaining twenty-two were secondary syphilitics, and fifteen were described as showing "pleozytose," while one had a positive Wassermann reaction in the cerebrospinal fluid.

Altmann and Dreyfus (1913) [1] made the first important contribution to the subject. These authors described cases with cells in the cerebrospinal fluid up to 15 per cubic millimetre as having "slightly altered" cerebrospinal fluids. These are not included in the following table of their results. No neurological examinations were made.

Stage of syphilis	Number of cases	Number with Wassermann reaction positive in blood	Number with cells over 15	Number with Wassermann reaction positive in cerebrospinal fluid
Primary	8 ..	2 ..	0 (One with 13 cells) (One with 7 cells) ..	0
Secondary with chancre ...	21 ..	21 ..	5 ..	0
Secondary without chancre	35 ..	35 ..	12 ..	11
Tertiary	2 ..	2 ..	0 ..	0
Latent	85 ..	46 ..	0 ..	0
,, ...	19 ..	19 ..	10 ..	10

With regard to the "latent" cases, all had been treated with mercury, but none presented themselves at the hospital for obvious syphilitic conditions. These authors also showed that the abnormality in the cerebrospinal fluid may be reduced by salvarsan treatment, although the number of cells may be temporarily increased after insufficient dosage.

In 1913 Ellis and Swift [6] published twenty-two cases of early untreated secondary syphilis. None of these showed any nervous lesions, but three had 12, 12 and 13 cells per cubic millimetre.

Gamper and Skutezky (1913) [12] also examined twenty-eight similar cases. Nine of these had over 10 cells per cubic millimetre in the cerebrospinal fluid, and of these, four had positive Wassermann reactions in the fluid.

In the same year Fildes and McIntosh [8] referred to twenty-three cases of syphilis, without signs of nervous disease, in whom the Wassermann reaction was negative in the cerebrospinal fluid. These

included all stages of syphilis except the primary. As was pointed out, however, these and other cases had been subjected to an elaborate neurological examination by Dr. H. Head and Dr. Fearnsides, and signs of nervous disease were found in several similar cases, which were then transferred to another category. Thus these results were not opposed to the findings of others.

In order to obtain a correct estimate of these abnormalities it is necessary to make routine examinations of all cases without selection, and such appear to have been first carried out by Engman, Buhman, Gorham and Davis (1913) [7].

Among other examples, these authors examined thirty-six cases of syphilis up to two years after infection. Four of these had a slight increase in cells, while three had increased cells, globulin and positive Wassermann reactions in the fluid. Of these three, two had symptoms of syphilis and one had unequal pupils.

During the two following years Wile and Stokes published several papers upon this subject [20, 21, 22]. These authors also made routine examinations of all syphilitics and laid special stress upon the occurrence of "neuroretinitis" and diminished bone conduction. For instance, in six cases of primary syphilis they described no less than five instances of "neuroretinitis." We have tabulated the findings in these six cases of primary syphilis as a sample of the results obtained.

Number of case	Duration of primary lesion (weeks)	Eye	Ear	Nervous system	Cells in cerebrospinal fluid	Wassermann
1	6	Normal	Normal	Normal	Normal	Negative
2	5	Neuroretinitis	,,	,,	7	Very slight positive
3	5	,,	,,	,,	5	Positive
4	4	,,	"Involved"	Rombergism, pupils sluggish and unequal.	200	Negative
5	1	,,	Normal	Knee and Ankle-jerks increased.	15	Negative
6	?	,,	Diminished bone conduction	Normal	5	Negative

It may be pointed out that these phenomena are not discussed in detail.

Hauptmann (1914) [14] examined fifteen cases of primary and secondary syphilis and found no abnormalities except in one case of

secondary syphilis. This showed increased reflexes and had sixty-nine cells with a negative Wassermann reaction in the cerebrospinal fluid.

Leopold (1914) [15] examined sixty-seven cases and found between 0 and 10 cells per cubic millimetre in forty-three and over 10 in eleven. The Wassermann reaction in the cerebrospinal fluid was positive in six of these. Routine neurological examinations were made and various slight abnormalities were found to be present.

Gutmann (1914) [13] examined fifty-seven cases of early syphilis and found one case of early secondary syphilis with 13 cells, and seven cases of secondary syphilis with increased cells, of whom two had a positive Wassermann reaction in the cerebrospinal fluid.

Audry and Lavau [2] also in the same year described a case of primary syphilis with 40 cells.

The most recent paper upon this subject, and also the largest series of cases, was published by With [23] in this Journal in 1918, although the paper was written two years earlier. His results may be tabulated as follows:—

Stage of syphilis	Number of cases	Number with positive Wassermann reaction in blood	Number with cells over 10	Number with Wassermann reaction positive in cerebrospinal fluid
Primary	45	0	1	1 (partial)
Primary	37	37	3	0
Secondary, early with rash, 3-5 months after infection	134	?	13	2
Secondary; later treated cases	41	?	4	1
Latent	41	41	4	2
Tertiary	18	?	1	0
	316		26	6

Thus in the categories mentioned With found over 12 per cent. with a pathological increase in the cells in the cerebrospinal fluid. The whole of this author's series included 439 cases of syphilis, but those already quoted are the only ones which bear upon this subject.

It may be remarked that there is no clinical description of the cases,[1] and thus it is difficult to satisfy oneself on the instance of primary syphilis with a slight positive Wassermann reaction in the cerebrospinal fluid. The serum was negative and there were no cells. It is also not quite certain to what extent this series is a purely random selection.

It will be recognized that many of these papers which have been referred to are in several respects unsatisfactory and fragmentary.

[1] This was furnished by the Author, but could not be printed owing to want of space,—EDITOR.

It has appeared to us that in order to emphasize the existence of an abnormality of the central nervous system, some writers have assumed a very narrow margin of safety. Several of the neurological abnormalities, for instance, are hardly definite enough to carry much weight in argument. Very much stress can hardly be laid upon a number of cells up to 10 per cubic millimetre in the cerebrospinal fluid. These findings may indeed be abnormal, but at the same time it appears to us to require more definite evidence before we accept without reserve Ravaut's statement that 62 per cent. of cases of secondary syphilis have abnormal central nervous systems.

Looking however at these findings as a whole, it is certain that a very considerable proportion of cases of early syphilis have *obviously* abnormal cerebrospinal fluids and a very much higher proportion *possibly* abnormal cerebrospinal fluids. It may also be said that very few of these show obvious signs of nervous disease such as would produce any disability, while many show no discoverable signs of disease at all.

The existence of these early and undeclared affections of the central nervous system in early syphilis is of the greatest importance. In 1914 McIntosh and Fildes [17] called particular attention to this subject in connection with the pathology of "parasyphilitic" affections. They argued that a tertiary syphilitic lesion such as a gumma was due to a recrudescence in a remnant of spirochætes which had remained dormant *in situ* since the generalization during the acute stage. As Lang had stated as long before as 1881, "an organ which is the seat of a gummatous lesion must have been affected in the early period of syphilis."

McIntosh and Fildes were engaged in showing that the lesions of "parasyphilis" differed in no essential particular from those of tertiary syphilis, and in order to complete the comparison it was necessary to show that the central nervous system, which later developed "parasyphilis," might readily have been affected in the early stages. They thus collected such evidence of nervous disease as was then to be found in the literature, and which has been referred to in this paper. They also noted that Hoffmann had demonstrated, by inoculation, *Spirochæta pallida* in the cerebrospinal fluid of an acute syphilitic, and called attention to the experimental work of Steiner, and Jacob and Weygandt, upon rabbit syphilis, which indicated that a lesion of the central nervous system was a common phenomenon in these animals soon after inoculation.

Clearly this subject has a very important bearing upon the treatment of syphilis.

If it is true that the infection of the central nervous system in the early stages may be the percursor of dementia paralytica in the later, it is important to determine the conditions under which this development takes place. The proportion of early cases which are affected is apparently large, and yet only a very small number of these develop dementia paralytica. The question thus arises, which of these early cases are likely to be affected in this way?

In ordinary tertiary syphilis there is reason to suppose that the patients so affected have remained actively syphilitic ever since the secondary stage, that they have had in fact more or less persistent positive Wassermann reactions. It is therefore legitimate to suggest provisionally that these cases, which subsequently develop dementia paralytica, have persistent reactions in their cerebrospinal fluids.

These matters are, however, merely speculative, and to be established a large number of observations are necessary over a period of years.

In order to study the subject more closely we have instituted an examination of the cerebrospinal fluid as a routine in all cases of syphilis, and hope to be able to follow some of these patients with a view to determining their subsequent fate.

II.—The General Nature of the Material, and Method of Dealing with It.

At Haslar every man who enters the venereal section for syphilis or suspected syphilis has the full details of his case entered upon a recording card system, which is designed to save labour and to give all information on a systematic plan suitable for mass statistics. Every man has all applicable laboratory tests carried out as a routine.

The treatment of the cases also proceeds upon routine lines, particular courses being applied to cases of particular "type." We do not treat men as individuals, but as "types" according to a set routine. The basis of the treatment is a series of injections of "neosalvarsan compounds,"[1] carried out at short intervals.

[1] Throughout this paper we refer to "neosalvarsan compounds" or "914," meaning any of the drugs of similar constitution, but different name, which are now upon the market. By "606" we mean salvarsan type drugs. Neither of these abbreviations include "galyl."

We have further instituted a system by which it is possible (if the exigencies of the Service permit) to follow the histories of all men after discharge to duty, and we hope that a sufficient number may be followed to throw important light upon the value of particular routine treatments in cases of a particular "type."

We do not give accessory forms of treatment, such as mercury, and endeavour to dissuade the medical officers in ships from giving it. We thus arrange a straight issue as to whether some five or six doses of a "neosalvarsan" drug are capable of curing a satisfactory percentage of men in the particular stage of the disease met with.

M. 207. (Established—March, 1918.) No.: *H. R. 385.*

A—— *B*——. Age *18.* Rtng.: *O. Sea.* Ship: *Minotaur.* Type: *C 1.*

Adm. *May 1, '18* Disch. *May 20, '18* Days Sick, *19* Infect. Date, *Mar 25, '18.*
Place, *Portsmouth.*

S. Pallida		Wassermann		Clinical Condition
Date	Result	Date	Result	Original:—
May 2, '18	*Pos.*	*May 4, '18*	*Pos.*	Present:—*Multiple indurated sores on and under prepuce. Ulcer to right of frænum. General adenitis. Papulo-squamous syphilide, trunk and limbs.* Previous treatment:—*None.* Condition on discharge:—*Sores healed; rash fading.*

Treatment			Subsequent History				
Date	Dose	Drug.	Date for W.R.	Ship	Result	Date	Remarks
May 3, '18	*0·45 grm.*	*N.A.B.*	*Aug. 1918*	*R.N.B. (Po)*	*Neg.*	*Aug. 11, '18*	
,, 6, ,,	,,	,,	*Nov.* ,,	*Renown*	*Neg.*	*Nov. 16,* ,,	
,, 9, ,,	,,	,,	*Feb. 1919*	,,	*Pos.*	*Feb. 8, '19*	*Wassermann*—relapse. Recalled
,, 12, ,,	,,	,,	*May* ,,				
,, 15, ,,	,,	,,	*Sept.* ,,				
,, 18, ,,	,,	,,	*Feb. 1920*				
			Aug. ,,				

C.S.F., *May 3, 1918. 4 lympho. per c.mm. W.R. neg.*

M. D. G. 13881/18. P.T.O.

Having established this routine system of examination and treatment (*vide* Fildes and Parnell [10]), we determined to investigate in a large series of cases the existence of unsuspected nervous disease,

such as has been recognized to exist in cases of syphilis during recent years. We hoped that if we were able to record the outstanding features of the state of the central system of every man, our "follow up" system might in the future throw important light upon the mechanism of the onset of the later nervous manifestations of syphilis.

We therefore instituted the system of examination described in the following pages with the assistance of colleagues who specialized in particular branches.

The preceding illustration of the obverse of the official card, filled up with a hypothetical case, will give an indication of the system of examination to which all men were subjected.

The number "H.R. 385" is the man's reference number, which is inscribed upon his syphilis papers which he carries with him. The letters denote that Haslar was the original treating hospital to which all subsequent specimens of blood for Wassermann tests must be sent. The "Type C. 1" indicates that the man was a "C." case—namely, secondary syphilis up to eighteen months from infection. The number "1" indicates the particular course of treatment applied. These "types" are used in the classification of the results of treatment. The date of infection is always recorded and, with judicious questions, can often be fixed accurately. The "treatment" column gives the treatment administered in the hospital. This example is the "1" course; the drug "N.A.B." is novarsenobillon.

The "subsequent history" section is of great importance. The "date for W.R." refers to the dates on which specimens of blood are to be sent in from ships and is automatically printed on the card with a rubber stamp. We allow for two years' observation.

In the "remarks" column we add recommendations which are sent with the report of the blood tests to the medical officers in the ships in which the man is then serving.

At the bottom of the card we add the results of the examination of the cerebrospinal fluid, and of the eyes, ears and nervous system when these are examined.

The reverse of the card shown opposite, deals with reinfections or relapses upon a similar plan.

We have made every effort to recall cases which have shown abnormalities of the central nervous system, for examination, but of course their return is dependent purely upon the exigencies of the Service. Upon discharge from hospital the men return to barracks, and from

there they are drafted back to ships. It is almost impossible to send men back from the Fleet, and therefore we are forced to make a re-examination while they are still at the barracks, and the period between treatment and re-examination is thus shorter than we should otherwise require. It will be seen that we have been able to make this re-examination in a proportion only of the total abnormal cases.

RELAPSE OR REINFECTION.

Clinical Condition :

TREATMENT			SUBSEQUENT HISTORY				
Date	Dose	Drug	Date for W.R.	Ship	Result	Date	Remarks

It should be particularly understood that in this investigation we have included every man who entered the venereal section from the end of January, 1918, to May 31, 1918—namely, 624 different cases. This is of special importance, because the series is a purely random selection and the results therefore indicate what may be expected from a similar random selection made elsewhere on similar material. We have in no sense accepted cases or endeavoured to obtain cases which might show interesting or abnormal results upon examination. The few men who have exhibited obvious signs of nervous disease have entered the section in a *bona fide* manner; the great majority of these, particularly all those who would be diagnosed as "tabes" or "general paralysis," are, of course, admitted into the neurological section of the hospital, with which we have no direct concern.

III.—The Routine adopted for the Examination of the Central Nervous System.

(1) *Classification of Cases.*

A classification of cases of syphilis into "stages," such as primary or secondary, does not convey to us any essential meaning, and therefore we have divided our material upon a time basis, or upon a basis which embraces a time and clinical factor. Thus our "division" of the cases is as follows:—

Division 1.—Cases in which *Spirochæta pallida* is found in an inoculation lesion, before the Wassermann reaction has become positive in the serum.

Division 2.—Cases, usually with an inoculation lesion, but with no other signs or history of general infection, except glandular enlargement and a positive Wassermann reaction, up to and including twenty-six weeks from the date of infection.

Division 3.—Cases with signs or history of general infection, including a positive Wassermann reaction up to and including eleven weeks from the date of infection.

Division 4.—Similar cases from twelve to twenty-six weeks inclusive after infection.

Division 5.—Similar cases over twenty-six weeks from infection.

Division 6.—Cases without signs other than a positive Wassermann reaction over twenty-six weeks from infection.

It will be observed that Divisions 1 and 2 include early and later cases of "primary" syphilis; Divisions 3 and 4 early and later cases of "secondary" syphilis; Division 5 still later cases of "secondary" and "tertiary" syphilis; while Division 6 includes "latent" cases.

It may be pointed out that some cases do not present conspicuous "primary" or "secondary" lesions, and thus could not be classified upon the ordinary basis of "stages." These we have dealt with purely upon a "time" basis.

It is sometimes particularly difficult to decide upon Division 2 or Division 6 when a man has merely a recently healed sore of uncertain nature, the date of infection with syphilis being then unobtainable.

We do not know whether such a man is a recent or an old case: whether he has not yet developed a more or less normal "rash," or whether he has passed the period when this should have appeared

and is not going to develop one. In the first instance he should be in Division 2 and in the second in Division 6. The distinction between the two depends almost entirely upon the duration of the infection.

(2) *Lumbar Puncture.*

(*a*) *Technique.*—When lumbar puncture is made part of the routine examination of every case of syphilis, it is necessary that the operation should cause little discomfort to the patient. Especially is this so in the instances where repeated examinations of a pathological cerebrospinal fluid are required. By using a technique that is practically painless it is not difficult for the operator to secure the confidence of the patient.

The following is the technique we employ: The patient is placed in a sitting posture with the back bowed and shoulders drooped. The skin is prepared by rubbing with ether and spraying with iodine. The skin around the selected interspinous space is then anæsthetized by injecting a 0·5 per cent. solution of novocain through a fine needle until a circular blanched raised area is obtained. Lumbar puncture is then carried out with a Barker's needle 3¼ in. long; 2 c.c. only of fluid are removed, and the patient is kept in bed for the remainder of the day. As a rule, the first prick of the fine needle is the only painful sensation, and no after-effects are felt; but a few cases have headaches, a feeling of stiffness in the neck and back of the head, or malaise, for one or two days, persisting sometimes for a week. The exact cause of these symptoms we do not know, but they are probably the result of a disturbance in the cerebral circulation. In an endeavour to prevent them, for a time we injected, through the lumbar puncture needle, an amount of sterile physiological salt solution equal to the amount of fluid removed, but headaches were not lessened, so this was abandoned. The best prophylactic we have found is rest in bed for the remainder of the day, and it is our custom not to give intravenous treatment on the day lumbar puncture is performed.

(*b*) *The estimation of the number of cells in the cerebrospinal fluid.*—The cell count requires to be done accurately. We have used throughout the method of Baker [3]. The following is the technique: Calibrate a pipette holding about 0·5 c.c. into five equal volumes. Shake the tube of recently drawn cerebrospinal fluid. Take up four volumes and then one volume of polychrome methylene blue (diluted 1 in 3 with water) and discharge them into a small test tube or centrifuge tube. Allow to stand for a minute or two and then after

shaking transfer a drop to a Thoma-Zeiss cell and cover in the usual way. Examine with a $\frac{1}{6}$-in. objective, and pull out the draw-tube until the diameter of the field is exactly eight of the smallest squares. Mark this point for future use. Count the cells in fifty fields with a mechanical stage and multiply this number by two. This will give the number of cells per cubic millimetre. If polymorphonuclear cells are seen the number is noted. If a small amount of blood is present, the number of red cells per cubic millimetre is estimated at the same time and one cell is deducted from the white cell count for every 1,000 red cells per cubic millimetre. This method is very accurate and rapid.

Some difficulty is always experienced in setting precise limits to the number of cells which may be considered normal. We have not ourselves examined a large number of normal persons to settle this point, but have taken the ordinarily accepted limits. Perfectly normal fluids do not in our opinion contain more than 2 or 3 cells per cubic millimetre; the majority indeed contain none, but we have taken up to 4 as being within physiological limits. We are not, however, prepared to assert that 6 cells is abnormal, because it is undesirable to over-estimate the number of pathological cases. We, therefore, have taken 10 cells as being an index of an abnormal condition, and in doing so follow a generally accepted practice. Those cases which have between 5 and 9 cells per cubic millimetre (both inclusive) we regard as "doubtful" and classify as such. At the same time we are of opinion that these "doubtful" cases are more likely to be abnormal than normal.

(*c*) *The Wassermann reaction in the cerebrospinal fluid and serum.*—The general technique adopted for carrying out this reaction is that of Fildes and McIntosh, described in this Journal [8]. Its later modification appears in the Interim Report upon the Wassermann Reaction by a Special Committee of the *Medical Research Committee*, upon the standardization of pathological methods [9]. The serum was always tested qualitatively in one dilution, while the cerebrospinal fluid was estimated quantitatively by the method of falling quantities of fluid. The largest amount of fluid used was 0·8 c.c. (tested with 0·5 c.c. of a 5 per cent. suspension of deposited sheep's corpuscles). The other quantities were 0·2 c.c., 0·05 c.c., and 0·012 c.c. The maximum quantity tested was four times that used in the work by McIntosh and Fildes, collaborating with Head and Fearnsides in this Journal [18]. The second dilution corresponds to the first in that investigation; the

third with the third, and the fourth with the fifth. There is, however, a difference in the technique used in the two investigations. While in the first the fluid was tested *unheated*, in the present the fluid is inactivated in the same way as the serum. We have made this modification because of the large amount of cerebrospinal fluid used in the present case. It has been remarked already [8] that a demonstrable difference may often be noticed between the Wassermann reaction in the cerebrospinal fluid from a case of "central syphilis" (G.P.I.) and "meningo-vascular syphilis." The reacting substance in the latter is more thermolabile than in the former. It was suggested that this is due to the presence of a transudate from the blood in the acuter meningo-vascular lesion. That is to say, the reacting substances in the cerebro-spinal fluid in the meningo-vascular lesion are derived from two sources —namely, the local diseased tissues and the blood. This blood may be a very disturbing factor if the fluid is unheated, since unheated serum, even from a non-syphilitic, is capable of giving a positive reaction in a high dilution, and when eight times as much fluid is used as serum in the test, the concentration of unheated serum would almost certainly be sufficient to affect the result in some cases.

In cases of early syphilitic meningitis we think that a considerable proportion of the reacting substance in the fluid is derived as a transudate from the blood, in the same way as a positive reaction is obtained in the case of syphilitics with meningococcal or tuberculous meningitis. If the fluid is tested in an unheated condition this serum transudate will give a much stronger reaction than it should if the man is syphilitic, or it may even give some inhibition if the man is non-syphilitic. Thus, with unheated fluid the transudate reaction is much exaggerated, and although more positive results may be obtained it appears to us that they will be less "specific" as a test of disease in the central nervous system.

The method of stating the results is the same as in the previous publications. The figure 4 which is an abbreviation of four plus signs (+ + + +) means that a complete inhibition of hæmolysis occurred with the quantity of test fluid to which the figure applied. Thus 4444 means, in the case of the cerebrospinal fluid, that complete inhibitions took place with 0·8 c.c.; 0·2 c.c.; 0·05 c.c.; and 0·012 c.c. of fluid. 4400 means that complete positive reactions took place with the first two quantities and negative with the last two. 4 - - - means that a complete reaction was obtained with the largest quantity, but the others were not tested. In the serum the figure 4 means that a positive reaction

was obtained with the ordinary test quantity of serum (0·1 c.c.). When reactions are not complete in any one case, the figures, 3, 2 or 1 are used to denote the degree of inhibition in that tube. When the results of examinations of serum and cerebrospinal fluid are expressed together, they are printed in the form of a fraction. The serum takes the place of the numerator and the cerebrospinal fluid of the denominator, thus: 4/4400.

(*d*) *Globulin and albumen tests.*—No globulin or albumen tests have been carried out in the cerebrospinal fluid of these cases, because, in view of the pressure of work, we did not desire to cumber ourselves with any tests which did not convey to us any more information than we had already gathered from the cell-count and Wassermann reaction. We have no doubt that the globulin and albumen tests are of value when other tests cannot be done, but they have always appeared to us to be somewhat indecisive.

(3) *The Examination of the Eyes.*

The eye-grounds were examined by Staff-Surgeon R. J. E. Hanson, O.B.E., F.R.C.S.Ed., R.N.V.R. Owing to pressure of work in the Ophthalmic Department, all cases with abnormal cerebrospinal fluids could not be investigated. Cases were selected, preference being given to those with high cell counts. No control cases were necessary.

(4) *The Examination of the Ears.*

Examination of the ears was largely carried out in the Venereal Section, with the co-operation of Temporary Surgeon E. C. Dunlop, R.N. One hundred unselected cases were used as controls: These consisted of fifty syphilis cases with normal cerebrospinal fluids, and fifty non-syphilis cases (persons who averred that they had never had syphilis, and whose sera were negative). In all cases Weber's, Rinne's and Schwabach's tests were applied. The object of the examination was to determine the condition of the internal ears. These tests could not be applied as a routine in all cases of syphilis. They were selected, but not to such a marked extent as with the eye examinations.

(5) *Examination of the Nervous System.*

The examination of the nervous system adopted as a routine could not be an elaborate one. In nearly every case with a positive cerebrospinal fluid we investigated:—

(*a*) The functions of the cranial nerves, except for taste and smell.

(*b*) The reflexes: (i) Pupils—to light and in accommodation, (ii) knee-jerks, (iii) ankle-jerks, (iv) elbow-jerks, (v) abdominal reflex, (vi) cremasteric reflex, (vii) plantar reflex, (viii) palate reflex. The organic reflexes, the state of the sphincters, and the intellectual functions were examined only in special cases with clinical nerve lesions.

(*c*) Sensory functions: (i) Sense of touch and pressure, (ii) sense of pain. These were tested with cotton wool for epicritic sense, and the point of a pin for protopathic sense. The temperature sense was not tested.

(*d*) Co-ordination. Romberg's sign.

IV.—The Results of the Examination of the Central Nervous System.

(1) *The Examination of the Cerebrospinal Fluid.*

(*a*) *General statement of the number of cases with abnormal cerebrospinal fluids.*—Six hundred and twenty-four cases of syphilis have been examined during this investigation; of these 115 exhibited a pleocytosis of 10 or more cells per cubic millimetre, while seventy-three came within the "doubtful" limit of 5 to 9 cells, both inclusive. That is to say, 18 per cent. of these cases were found to have a definite pleocytosis and 11 per cent. came within the "doubtful" limits. If, as seems justifiable, the "doubtfuls" are considered to be abnormal and are included with the "positives," it is seen that 30 per cent. of these men were abnormal in this respect. With regard to the Wassermann reaction, we found forty-one with positive reactions in the cerebrospinal fluid (6 per cent.). In all except one of these, the cells were also positive, and thus the total number of abnormal cases is increased by one only. The Wassermann reaction was not positive in any instance of "doubtful" pleocytosis.

(*b*) *The incidence of pleocytosis in the various divisions of the cases.*—When the abnormal cases in the different divisions are tabulated, it is seen that the incidence is greater in some than in others.

From this table it appears that a pleocytosis exists in a small number of cases of primary syphilis, even before the Wassermann reaction in the serum has become positive, and that the number gradually increases until what may be described as the later secondary

period, when no less than 29 per cent. are affected. During the later stages (tertiary), with manifest signs, the number affected is considerably smaller, but in the "latent" period, when manifest signs are absent, there is a very marked increase in the number of cells. The "doubtful" pleocytosis does not show this variation according to the stage of the disease.

TABLE SHOWING THE INCIDENCE OF ABNORMALITY IN THE DIFFERENT DIVISIONS.

Division	Number of cases	Number with positive cells	Number with "doubtful" cells
1	71	2	9
2	168	15	17
3	107	18	11
4	85	25	11
5	78	14	11
6	115	41	14
Results expressed as percentage of cases.			
1	..	2	12
2	..	8	10
3	..	16	10
4	..	29	12
5	..	17	14
6	..	35	12

It is desirable to illustrate the degree of abnormality met with in these cases with examples; we have therefore selected the following instances in the various divisions.

Division 1.

Case 845.—Infected January, 1918. *S. pallida* positive, March 16, 1918. Examined March 17: Ulcer in coronal sulcus; general adenitis; 16 L., W.R. 0/0,[1] N. normal, B. normal, O. not examined, S. normal.

Case 1195.—Infected March 28, 1918. *S. pallida* positive, April 27. Received 0·3 grm. galyl on April 28 and 0·25 grm. on May 8. Examined

[1] Throughout this paper for economy of space we use the following symbols:—
16 L. = 16 lymphocytes per c.mm.; 16 L. + 2 P. = 16 lymphocytes and 2 polymorphs.
0 = negative Wassermann reaction (W.R.), using the largest quantity of test fluid.
4 = positive W.R.; 3 or 2 incomplete positive W.R., using the largest quantity of test fluid.
4 - - -; 4444; 4440; 4400 or 4000 = positive W.R. in the cerebrospinal fluid, using the full quantity (0·8 c.c.) only, or 0·8 c.c., 0·2 c.c., 0·05 c.c., and 0·012, as the case may be. When the result of the examination of serum and cerebrospinal fluid is given together, it is expressed as a fraction thus: 4 (serum) /4400 (C.S.F.).
N = physical signs of nervous disease.
B = bone conduction or otological examination.
O = ophthalmological examination.
S = symptoms of nervous disease.
606 = salvarsan type compounds } other than galyl.
914 = neo-salvarsan type compounds }
— = no observation.

May 11: Indurated ulcer at meatus; general adenitis; 8 L., W.R. 0/0, N. normal, B. normal, O. not examined, S. normal.

Division 2.

Case 986.—Contracted syphilis in June, 1916. Re-infected March 7, 1918. Sore on penis two days later. *S. pallida* positive, March 19, 1918. Examined April 11, 1918: Scar of recent sore on prepuce; scar of old sore in coronal sulcus; general adenitis; 114 L. + 2 P., W.R. 0/0, N. normal, B. normal, O. normal, S. normal.

Case 838.—Infected December 26, 1917. Examination on March 16, 1918: Kidney-shaped ulcer at junction of penis and scrotum, left side; *S. pallida* positive; general adenitis, also gonorrhœa; 8 L., W.R. 4/0, N. normal, B. normal, O. not examined, S. not inquired into.

Division 3.

Case 1230.—Infected about the middle of March, 1918. Had 0·25 grm. galyl, May 8, 1918. Examined May 12, 1918: Scar of sore on prepuce; sore on under surface of prepuce near edge, causing phimosis; general adenitis; fading macular syphilide; 16 L., W.R. 4/0, N. normal, B. diminished on both sides, O. not examined, S. dizziness for ten days.

Case 1238.—Infected March 10, 1918. Examined May 12, 1918: Scars of numerous erosions on glans, fading papulo-macular syphilide, general adenitis, condylomata ani; iridocyclitis right and left; 8 L., W.R. 4/0, N. normal, B. diminished on both sides, O. iridocyclitis, S. none.

Division 4.

Case 251.—Infected September 29, 1917. Examined November 29, 1917: Indurated ulcer on prepuce and indurated sore on lower lip; *S. pallida* positive in penile and lip sores: general adenitis; papular syphilide; Wassermann positive; had 3·15 grm. of "914" between November 29, 1917, and January 12, 1918 (the course being interrupted between December 3 and January 3 for unavoidable reasons). Re-admitted on April 1, 1918, with the following signs of relapse: Scar of sore on lip vesicular and about to break down; healing sore at frænum which was destroyed; general adenitis; papular syphilide; 352 L + 10 P., W.R. 4/4400, N. normal, B. diminished in both ears, O. not examined, S. none.

Case 555.—Infected in September, 1917. Sore on penis and rash. Examined on February 1, 1918: Scar of above sore; headaches and occasional giddiness, when stooping down, for one month; 750 L. + 144 P., W.R. 4/4000, N. normal, B. not examined, O. abnormal (*vide* p. 286), S. as above.

Division 5.

Case 1274. Infected in 1903. History of penile sore only. In 1914 had ulcers on back of right calf. Examined May 15, 1918: Inguinal and axillary adenitis; healing gummatous syphilodermia on anterior and internal aspects of

right leg; scars of serpiginous ulcers with pigmented edges on posterior aspect of right calf and outer aspect of left knee; 200 L., W.R. 4/4400, N. normal, B. diminished on both sides, O. abnormal (*vide* p. 287), S. none.

Case 1297.—Infection date uncertain. Gonorrhœa in 1913 and in 1914. Examined May 27, 1918: General adenitis; patches of late syphilodermia on both palms, right knee, right thigh and alæ nasi; scars of recent ulcers on fauces; 8 L., W.R. 4/0, N. normal, B. diminished on both sides, O. not examined; S. none.

Division 6.

Case 825.—Infected 1903. Had penile sore, rash and sore throat. Examined March 13, 1918: Scar of sore on glans; scars of more recent ulcers on penis; 26 L., W.R. 4/0, N. abnormal (*vide* p. 282), B. not examined, O. not examined, S. present (*vide* p. 282).

Case 1175.—Infected September, 1917. Had sores under prepuce. Had two doses of galyl March 26 and April 5. Examined May 9, 1918: Scars of recent sores on prepuce; 8 L., W.R. 4/0, N. normal, B. normal, O. not examined, S. none.

Case 1164.—Infected September, 1917. Had penile sore, rash, sore throat. Had two injections of galyl March 9 and April 9, 1918, also three injections of mercury. Examined May 6, 1918: General adenitis; fading macular syphilide on both forearms; 1100 L., W.R. 4/4410. Had 4·65 grm. "914" between May 8 and June 17, 1918. After having had two doses of 0·45 grm. at three-day intervals, paralysis of the right sixth cranial nerve developed, but the treatment was not interrupted. June 20, 1918: 30 L., W.R. 0/4000. Had 1·8 grm. "914" between June 24 and July 8. July 16, 1918: 30 L., W.R. 0/3000. Paralysis of sixth nerve not completely resolved, but much improved.

(*c*) *The question of previous treatment affecting results.*—It has been suggested from time to time that the pleocytosis which had been recognized in these early cases of syphilis was associated with salvarsan or arsenical treatment. Finger, for instance, suggested that salvarsan had a direct toxic action upon the central nervous system, while others held, and still hold in some cases, that salvarsan predisposed to syphilitic affections of the central nervous system, and thus pleocytosis was common after this treatment as a "provocative" effect. In order to estimate the importance of this factor we have divided our cases into "untreated" and "recently treated." We have only taken those cases treated with an arsenical compound within fourteen days as "recently treated," since this is the period in which the "provocative reaction" is best detected in the serum or cerebrospinal fluid in the case of the Wassermann reaction.

TABLE SHOWING THE ABNORMALITY IN UNTREATED AND RECENTLY TREATED CASES.

Untreated.

Division	Number of cases	Number with pleocytosis	Number with "doubtful" pleocytosis
1	43	1	5
2	132	13	16
3	96	14	18
4	67	18	9
5	47	5	6
6	55	19	6
	440	70 (= 15 per cent.)	60 (= 13 per cent.)

Recently Treated.

1	24	1	3
2	24	1	1
3	10	3	2
4	8	3	2
5	6	3	1
6	6	1	1
	78	12 (= 15 per cent.)	10 (= 12 per cent.)

From this table it is clear that arsenical treatment carried out during the period most satisfactory for inducing provocative reactions has no such effect. The incidence of abnormality is almost exactly the same in the untreated and recently treated cases. Thus we may conclude that this abnormality is in no way associated with previous arsenical treatment. On the other hand, if our results are compared with those of some others and found to be less abnormal, it may be objected that treatment had reduced the number of abnormal reactions. Few of our cases had, however, received any extensive course of treatment with arsenical compounds before coming under observation, but nevertheless we tabulate them to show the importance of this fact or factor.

TABLE SHOWING THE EFFECT OF TREATMENT (NOT RECENT) UPON THE INCIDENCE OF ABNORMALITY.

Cases treated, but not within fourteen days.

Division	Number of cases	Number with pleocytosis	Number with "doubtful" pleocytosis
1	4	0	1
2	13	2	0
3	1	1	0
4	10	4	0
5	25	6	4
6	53	20	7
	106	33 (= 31 per cent.)	12 (= 11 per cent.)

The untreated cases shown in the table on this page had 15 per cent. with pleocytosis, and 13 per cent. with "doubtful" pleocytosis; thus the treated cases exhibited a considerably greater degree of abnor-

mality. This result may be taken as confirming the view that cases after salvarsan treatment show a greater incidence of nervous disease than cases after no treatment; but this would be an incorrect deduction. The high percentage affected in the treated cases is due to the large proportion of Division 6 cases which appear in the list in the above table. Taking Division 6 alone, there is no greater incidence of nervous diseases in the treated than in the untreated.

The reason for the large proportion of treated Division 6 cases is no doubt that these men, having been formerly admitted to a hospital for treatment, have come under the Naval "follow up" routine, and thus had Wassermann reactions carried out more often than men who had never been to hospital. Then, being found with positive reactions after the almost invariably inefficient treatment, they were again admitted for examination.

In general we conclude that the amount of treatment which our patients received had no effect upon our results one way or another.

(*d*) *The incidence of a positive Wassermann reaction in the cerebro-spinal fluid in the various divisions of the cases.*—It is of importance to determine the stage of the disease in which the Wassermann reaction is most commonly present and at which the nervous lesion first becomes sufficiently pronounced to establish a positive reaction in the cerebro-spinal fluid.

TABLE SHOWING THE INCIDENCE OF POSITIVE WASSERMANN REACTIONS IN THE CEREBRO-SPINAL FLUID IN THE VARIOUS DIVISIONS OF THE DISEASE.

Division	Number of cases	Number with positive W.R.	Number per cent. with positive W.R.
1	71	0	0
2	168	1	0
3	107	3	2
4	85	7	8
5	78	5	6
6	115	26	22

In this table it is seen that the positive reaction is not observed in primary syphilis until the Wassermann reaction in the serum has become positive (Division 2), but even then there is only one instance of a very slight reaction.

Case 513.—Infected September, 1917. Examined January 25, 1918. Indurated scar of recent sore on dorsum of penis; general adenitis; 84 L., W.R. 4/2000, N. not examined, B. not examined, O. positive (*vide* p. 285), S. not examined.

In the course of the routine clinical examination of cases, three men were placed in Division 2 who have since been transferred to Division 6. These three men had positive Wassermann reactions in

the cerebrospinal fluid. We give here the details in order to justify ourselves and illustrate the difficulties of diagnosis.

Case 1130.—Mercantile Marine stoker, aged 38. Infected "during the last six weeks." Had a sore on the penis sixteen years before. Examined May 4, 1918: Indurated subpreputial ulcer dorsally; general adenitis; gonorrhœa; no *S. pallida* found on three occasions, but antiseptics had been applied; 18 L., W.R. 4/4- - -, N. normal, B. normal, O. not examined, S. general malaise for ten days before admission.

Case 1281.—Chief Petty Officer, aged 42. Said to have been infected March 10, 1918. Examined April 23, 1918: scars of papules on glans; slight general adenitis; 12 L., W.R. 4/4- - -, N. normal, B. normal, O. positive (*vide* p. 288), S. normal.

Case 1059.—Stoker, aged 23. Infected July, 1915 (primary syphilis). W.R. positive in August and December, 1915; negative in June, 1916. Treated with mercury and one dose of "606." (?) Reinfected December 15, 1917. (?) *S. pallida* found February 26, 1918. Examined April 20, 1918: Acquired phimosis; balanitis; no gonorrhœa; subpreputial induration; general adenitis; 42 L., W.R. 4/4400, N. normal, B. normal, O. positive (*vide* p. 287), S. normal.

These three cases had penile sores, and the question to be decided was, whether these were primary syphilis or non-syphilitic lesions in old syphilitics. The spirochæte test should be the deciding factor in such cases, but in one (Case 1281) the lesions had healed, in another (Case 1130) *S. pallida* could not be found, while in the third they were said to have been found outside this hospital, but we are not satisfied that this diagnosis was correct. This man had phimosis and balanitis with a thick yellow discharge, incorrectly diagnosed as gonorrhœa. Under such circumstances the differential diagnosis of *S. pallida* from *S. refringens* may be extremely difficult, and we have frequently known mistakes to have been made.

In the absence of the spirochæte test we may have recourse to clinical examination, and in only one was there serious clinical evidence of primary syphilis—namely, an "indurated subpreputial ulcer dorsally"; but we may remark that too much diagnostic value should not be placed upon "induration."

As regards evidence to establish the fact of these men being old syphilitics, this is forthcoming in two. One undoubtedly had syphilis shortly before, while another stated that he had a sore sixteen years ago. Two of the men were old seamen, and were of an age which suggests an older infection.

Our attitude towards these cases is that there is no certain evidence

that they belong to Division 2, and if the evidence is fairly equally balanced we prefer to transfer them to Division 6, because otherwise they would be the only examples of a fully positive Wassermann reaction in the earlier division; such pronounced nerve lesions and eye lesions in a case of primary syphilis would be so remarkable that they should be established beyond a doubt before they are accepted.

In Division 3 the nervous lesion may be sufficiently advanced to give a few undoubted reactions in the cerebrospinal fluid.

Case 593.—Infected in November, 1917. Examined February 5, 1918. Scar of sore to right of frænum; marked general adenitis; both tonsils enlarged and covered with mucous patches: scars of recent condylomata ani. 740 L. + 2 P.; W.R. 4/4300, N. normal, B. normal, O. abnormal (*vide* p. 285), S. none.

Case 1258.—Infected early in April, 1918. Examined May 12, 1918. Scars of large ulcers on body of penis left. Two erosions, one on dorsum of glans left, and one subpreputial left. General adenitis; ulcers on tonsils: rhagades at left angle of mouth; follicular syphilide; 36 L., W.R. 4/4---, N. normal, B. positive, O. not examined, S. hard of hearing for several years, worse last month. Treatment, from May 18 to June 2, 2·7 grm. "914." Re-examined July 23, 1918: 0 L., W.R. 4/0.

Case 673.—Infected 1916. Primary syphilis treated with three doses of galyl. Reinfected January 29, 1918. Examined February 21, 1918: Small sore on penis to right of meatus; *S. pallida* present; condylomata ani; general adenitis; 82 L., W.R. 4/3000, N. not examined, B. not examined, O. normal, S. not inquired into.

In the later secondary period (Division 4) positive reactions are frequent, but rather less so in the manifest tertiary (Division 5).

The latent period (Division 6) shows the most remarkable result, no less than 22 per cent. of such cases being affected in this manner. We give here three ordinary examples:—

Case 829.—Infected May, 1914. Indurated sore at meatus. Treated with 0·3 grm. "606" in May, 1914, and three doses of galyl between July and September, 1917; also mercurial injections and pills. Examined March 17, 1918: No lesions; 98 L., W.R. 4/4400, N. normal, B. diminished right, O. abnormal (*vide* p. 287), S. not inquired into.

Case 520.—Infected May, 1916. Had two injections of galyl in May, 1916, and 0·75 grm. "914" in June, 1917. Examined January 25, 1918: General adenitis; 107 L., W.R. 4/4440, N. normal, B. diminished on right side, O, abnormal (*vide* p. 287), S. none. Had 4·5 grm. "914" between January 27 and March 10, 1918. On March 11, 1918: 16 L., W.R. -/4---. On June 8, 1918: 10 L., W.R. 0/0.

Case 740.—Infected November, 1916. Sore on penis, rash, sore throat. Had three injections of galyl, May and June, 1917, and twelve injections of

mercury. Examined February 28, 1918: Scars of subpreputial sores; inguinal and cervical adenitis; 112 L.. W.R. 4/4000. Had 3·6 grm. "914" between February 28 and March 28 (four doses of 0·9 grm.). April 11, 1918: 10 L., W.R. -/3000, and 0·9 grm. "914" given. May 9, 1918: 10 L., W.R. 4/3000, and given 0·9 grm. "914" on the following day.

(*e*) *The relation of the degree of pleocytosis to the incidence of the Wassermann reaction in the cerebrospinal fluid.*—It is of interest to inquire whether a positive Wassermann reaction has any constant association with a particular degree of pleocytosis in the fluid. In the following table all cases with a positive Wassermann reaction are arranged with the number of cells and compared with the number of cases which gave a negative reaction.

TABLE SHOWING THE RELATION OF THE POSITIVE WASSERMANN REACTION IN THE CEREBROSPINAL FLUID TO THE NUMBER OF CELLS.

Number of cells in the C.S.F.	Number of cases with W.R. pos.	Degree of reaction	Number of cases with W.R. 0
0—9	1	4--- (0 cells)	508
10—19	3	4--- (12 ,,)	36
		4--- (14 ,,)	
		4--- (18 ,,)	
20—49	4	4---	26
		4400	
		4---	
		4---	
50—99	11	4400	6
		4400	
		4000	
		3000	
		2000	
		4---	
		4400	
		4400	
		4100	
		4400	
		4400	
100—149	7	4400	3
		4400	
		4400	
		4400	
		4440	
		4000	
		4400	
150—199	4	4400	2
		4400	
		4400	
		4400	
200—299	4	4400	0
		4444	
		4---	
		4000	
300—499	2	4400	1 (476 cells)
		4400	
500—999	3	4300	0
		4100	
		4---	
1000—	3	4400	0
		4---	
		4410	

This table shows that in 509 cases without pleocytosis only one was observed with a positive Wassermann reaction. That is to say, it is very uncommon to observe a positive reaction when there are no cells. This rule does not of course apply when dealing with ordinary cases of cerebrospinal syphilis, when they have been subjected to extensive treatment; but practically none of our cases had been so treated with the exception of this single instance in Division 5.

Case 88.—Infected 1907. Original symptoms and treatment not recorded. On November 9, 1917, admitted to hospital on account of a positive Wassermann reaction. General adenitis (old fibrous type) and scars of ulcers on both legs. Between November, 1917, and January, 1918, he received 2·7 grm. "914." On April 15, 1918, readmitted with bilateral eighth-nerve deafness; 0 L., W.R. 4/4- - -.

Among thirty-nine cases with a slight degree of pleocytosis (ten to nineteen cells) three were found with a positive Wassermann reaction. One of these (No. 627) was an old case of syphilis, and two were probably[1] old cases in the latent stage.

As the number of cells in the cerebrospinal fluid increases so do positive Wassermann reactions become more frequent. When there are over 200 cells per cubic millimetre a positive reaction appears to be almost constant. In thirteen instances only one had a negative reaction.

Case 1135.—Infected end of December, 1917. Examination May 4, 1918: Scars of multiple indurated small ulcers in coronal sulcus and on under surface of prepuce; *S. pallida* not found twice, but local antiseptics had been applied; general adenitis; gonorrhœa; 476 L., W.R. 3/0000, N. normal, B. normal, O. abnormal (*vide* p. 285), S. normal. One week later the Wassermann reaction in the serum was negative.

This case has been classed in Division 2, primary syphilis with a positive Wassermann reaction; but it is impossible to say whether this classification is correct, owing to the fatal practice of applying local antiseptics before spirochætes have been looked for.

It is clear from these results that positive reactions become more frequent as the number of cells increase. While only one in 509 is positive when there are between 0 and 9 cells, three out of three are positive when there are 1,000 cells.

(*f*) *The occurrence of S. pallida in the cerebrospinal fluid.*—In order to obtain final proof that the abnormalities of the cerebrospinal fluid

[1] *Vide* p. 277 for discussion of these two cases, Nos. 1130 and 1281.

were due to syphilis, several with the highest cell counts were examined for *S. pallida*. Thirteen of these contained over 200 cells per cubic millimetre, and the following technique was used: The 2 c.c. of fluid was placed in a small sterile glass tube, having a test tube end and a diameter of 1 cm. This was centrifuged at high speed for fifteen minutes. The fluid was then gently poured off, to be kept for a Wassermann test, leaving a deposit sticking to the bottom. Keeping the mouth of the tube downwards, the deposit was taken up in a capillary pipette with a rubber teat attached and placed under a cover-slip on a glass slide. It was then examined by dark-ground illumination. Fifteen cases were examined, in every instance within three hours after lumbar puncture, and in one only was *S. pallida* found. This man (Case 548, pp. 281 and 293) was infected twenty weeks previously, and had 1,000 cells in the cerebrospinal fluid.

(2) *The Results of the Examination of the Motor and Sensory Functions of the Central Nervous System.*

The number of cases which showed clinical evidence of abnormality of the central nervous system may conveniently be summarized by the following table:—

Division of disease	Number of cases with abnormal C.S.F.	Number of cases examined neurologically	Number of cases with clinical evidence of disease in the C.N.S.	Number of cases with symptoms	Number of cases with clinical signs
1	2	2	0	—	—
2	15	11	0	—	—
3	18	15	1	1	0
4	25	23	7	6	2
5	15	12	5	4	3
6	41	36	10	9	3

The details of the abnormalities detected in every case are as follows:—

Division 3.

Case 1230.—Dizziness for ten days.

Division 4.

Case 139.—Complained of weakness in his legs after walking.

Case 548.—For one month he had noticed that sometimes he was dizzy for a few moments after rising from a chair. He had been doing full duty in his ship until he came to hospital on account of his rash. He had no other symptoms, but his cerebrospinal fluid contained 1,000 cells per cubic millimetre.

Case 555.—For two months he had headaches and occasional giddiness after stooping down.

This table shows that in 509 cases without pleocytosis only one was observed with a positive Wassermann reaction. That is to say, it is very uncommon to observe a positive reaction when there are no cells. This rule does not of course apply when dealing with ordinary cases of cerebrospinal syphilis, when they have been subjected to extensive treatment; but practically none of our cases had been so treated with the exception of this single instance in Division 5.

Case 88.—Infected 1907. Original symptoms and treatment not recorded. On November 9, 1917, admitted to hospital on account of a positive Wassermann reaction. General adenitis (old fibrous type) and scars of ulcers on both legs. Between November, 1917, and January, 1918, he received 2·7 grm. "914." On April 15, 1918, readmitted with bilateral eighth-nerve deafness; 0 L., W.R. 4/4- - -.

Among thirty-nine cases with a slight degree of pleocytosis (ten to nineteen cells) three were found with a positive Wassermann reaction. One of these (No. 627) was an old case of syphilis, and two were probably[1] old cases in the latent stage.

As the number of cells in the cerebrospinal fluid increases so do positive Wassermann reactions become more frequent. When there are over 200 cells per cubic millimetre a positive reaction appears to be almost constant. In thirteen instances only one had a negative reaction.

Case 1135.—Infected end of December, 1917. Examination May 4, 1918: Scars of multiple indurated small ulcers in coronal sulcus and on under surface of prepuce; *S. pallida* not found twice, but local antiseptics had been applied; general adenitis; gonorrhœa; 476 L., W.R. 3/0000, N. normal, B. normal, O. abnormal (*vide* p. 285), S. normal. One week later the Wassermann reaction in the serum was negative.

This case has been classed in Division 2, primary syphilis with a positive Wassermann reaction; but it is impossible to say whether this classification is correct, owing to the fatal practice of applying local antiseptics before spirochætes have been looked for.

It is clear from these results that positive reactions become more frequent as the number of cells increase. While only one in 509 is positive when there are between 0 and 9 cells, three out of three are positive when there are 1,000 cells.

(*f*) *The occurrence of S. pallida in the cerebrospinal fluid.*—In order to obtain final proof that the abnormalities of the cerebrospinal fluid

[1] *Vide* p. 277 for discussion of these two cases, Nos. 1130 and 1281.

were due to syphilis, several with the highest cell counts were examined for *S. pallida*. Thirteen of these contained over 200 cells per cubic millimetre, and the following technique was used: The 2 c.c. of fluid was placed in a small sterile glass tube, having a test tube end and a diameter of 1 cm. This was centrifuged at high speed for fifteen minutes. The fluid was then gently poured off, to be kept for a Wassermann test, leaving a deposit sticking to the bottom. Keeping the mouth of the tube downwards, the deposit was taken up in a capillary pipette with a rubber teat attached and placed under a cover-slip on a glass slide. It was then examined by dark-ground illumination. Fifteen cases were examined, in every instance within three hours after lumbar puncture, and in one only was *S. pallida* found. This man (Case 548, pp. 281 and 293) was infected twenty weeks previously, and had 1,000 cells in the cerebrospinal fluid.

(2) *The Results of the Examination of the Motor and Sensory Functions of the Central Nervous System.*

The number of cases which showed clinical evidence of abnormality of the central nervous system may conveniently be summarized by the following table:—

Division of disease	Number of cases with abnormal C.S.F.	Number of cases examined neurologically	Number of cases with clinical evidence of disease in the C.N.S.	Number of cases with symptoms	Number of cases with clinical signs
1	2	2	0	—	—
2	15	11	0	—	—
3	18	15	1	1	0
4	25	23	7	6	2
5	15	12	5	4	3
6	41	36	10	9	3

The details of the abnormalities detected in every case are as follows:—

Division 3.

Case 1230.—Dizziness for ten days.

Division 4.

Case 139.—Complained of weakness in his legs after walking.

Case 548.—For one month he had noticed that sometimes he was dizzy for a few moments after rising from a chair. He had been doing full duty in his ship until he came to hospital on account of his rash. He had no other symptoms, but his cerebrospinal fluid contained 1,000 cells per cubic millimetre.

Case 555.—For two months he had headaches and occasional giddiness after stooping down.

Case 560.—Weakness of facial muscles on left side.

Case 958.—Insomnia, nocturnal headache, vertigo.

Case 1056.—Complete bilateral paralysis of facial muscles. Weakness of the left external rectus muscle.

Case 1098.—Complained of unusual languidness.

Division 5.

Case 384.—Complained of diplopia for one month. He had ptosis of right eyelid.

Case 607.—Complained of headaches.

Case 840.—He had had spells of dizziness, during which he would have to support himself for a few moments; ankle-jerks absent.

Case 956.—Had difficulty in swallowing both fluids and solids for three months prior to entry. The throat was normal, and the symptoms disappeared completely after treatment.

Case 1071.—Paralysis of facial muscles on left side. Diminished sensation over area supplied by the fifth cranial nerve on the left side.

Division 6.

Case 125.—He complained of headaches and was very sleepy during the day. He easily got tired.

Case 627.—Headaches for three months before admission to hospital.

Case 753.—He had felt "drowsy" (the reason he reported sick) during the past six months.

Case 767.—For one year he had loss of memory, inability to concentrate, and was easily worried.

Case 825.—One year before admission he had numbness of the arms. On examination he had weakness of facial muscles on the left side.

Case 1064.—For four months has had frontal headaches and insomnia. Memory for recent events was poor.

Case 1084.—He complained of insomnia.

Case 1137.—For the past nine months he had attacks of unconsciousness and of severe vertigo lasting for several minutes.

Case 1141.—He complained of deafness for "women's voices."

Case 1142.—He complained of defective vision and diplopia. He had paralysis of left external rectus muscle.

The central nervous system was also examined in twenty-two cases in which the cerebrospinal fluid contained from 5 to 9 cells per cubic millimetre—i.e., "doubtful" cases. These included cases from each of the six divisions. In only one (Case 771, Division 3) was any abnormality found.

Case 771.—Infected December 18, 1917. Examined March 7, 1918: Balanitis: acquired phimosis; subpreputial sores; general adenitis; lenti-

cular syphilide; 8 L., W.R. 4/0, N. normal, B. normal, O. not examined, S. occipital headache for nine days.

(3) *The Results of the Examination of the Function of the Internal Ears.*

The results of these examinations may be summarized as follows :—

TABLE SHOWING THE NUMBER OF CASES WITH ABNORMALITIES OF THE INTERNAL EARS. (DIMINISHED BONE CONDUCTION.)

Division	Number of cases with abnormal C.S.F.	Number of cases examined for internal ear function	Number of cases with internal ear function abnormal	Number of cases with bone conduction diminished on right side only	Number of cases with bone conduction diminished on left side only	Number of cases with bone conduction diminished on both sides
1	2	2	0	—	—	—
2	15	10	2	0	1	1
3	18	12	4	0	1	3
4	25	19	7	0	0	7
5	15	10	4	0	1	3
6	41	26	13	4	2	7

Of nineteen "doubtful" cases whose ears were examined six were found to be abnormal. Of these, two were in Division 2, and one in each of the other divisions, excepting Division 5. Thus, taking "positive" and "doubtful" cases together, thirty-six were found to be abnormal out of ninety-eight (36 per cent.).

As already stated, however, we determined to carry out a series of control examinations before drawing conclusions from these results. We first examined fifty men who stated that they had never had syphilis, showed no signs of syphilis, and gave a negative Wassermann reaction. Of these no less than fifteen showed diminished bone conduction, that is to say, a proportion practically as high as among the syphilitics. In six of these cases the abnormality was to be accounted for by gun fire, but among the others no sufficient cause was apparent.

We also examined fifty syphilitics with normal cerebrospinal fluids, and twenty-nine of these were found to have diminished bone conduction. Gun fire was probably responsible for the lesion in thirteen of the cases.

In view of the large number of "positives" among the controls, therefore, we are not prepared to lay much stress upon the value of this test and have now discontinued it.

(4) *The Results of the Examination of the Eyes.*

The following table shows the degree of abnormality met with during the ophthalmological examinations:—

TABLE SHOWING THE NUMBER OF CASES WITH ABNORMALITIES OF THE EYES.

Division	Number of cases with abnormal C.S.F.	Number of cases whose eyes were examined	Number of cases with abnormal eyes
1	2	0	—
2	15	3	3
3	18	8	5
4	25	13	9
5	15	7	6
6	41	22	17

No examination of the eyes was made in cases whose cerebrospinal fluid showed "doubtful" cells.

Staff-Surgeon Hanson has been able to recognize a number of extremely slight but none the less perfectly definite abnormalities in the eye grounds, which probably represent the same condition as that which Zaloziecki and Frühwald noticed and did not recognize when they called it a "pseudoneuritis." Staff-Surgeon Hanson looks upon these abnormalities as representing early stages in the development of the syphilitic choroidal endarteritis and retinitis which is well known in later stages of the disease.

These early ocular changes contrast with those found in later stages with sectorial or insular scotomata the result of postchoroido-retinitic atrophy.

NOTES UPON THE OCULAR CONDITIONS, BY STAFF-SURGEON R. J. E. HANSON, R.N.V.R.

"Retinitis ex Lue" (Early Stage).

Typical signs.—The conditions vary in their intensity, but three types of signs in the fundus oculi were noted:—

(1) *Hyperæmia.*—The retinal venules especially were over-full.

(2) *Engorgement.*—Enlargement and cloudy appearance of the perivascular lymph spaces around the retinal vessels and around the papilla. (Luetic halo.)

(3) *Pigment overgrowth and disturbance of the retina.*—Small rounded woolly-looking opacities with fine spidery connective tissue changes, without apparent upset to the functions of the rods and cones.

In relation to No. 2 above, it is interesting to recall that there are physical and chemical changes in the cerebrospinal fluid, and that this is

intimately connected with the subarachnoid contents, and these last with the retinal lymph-streams.

With regard to No. 3 above, one recalls the extensive pigmentation changes in the skin lesions of the secondary stage.

Summary.—There was little evidence of interference with function—i.e., with fields, form-sense, light difference, and colour thresholds. No alterations in the fundus oculi were observed in the cases seen shortly after the appearance of the inoculation lesion. In the later cases the changes in the fundus oculi were :—

(1) Symmetrical.

(2) Mainly peripheral.

(3) Diffuse and not circumscribed—i.e., not more marked nor intense at one part of the periphery than another.

No hyalitis nor choroiditis was observed but an underlying condition of choroidal endarteritis may be present in these cases of stippling of the fundus oculi.

The detailed reports of the examination of the eyes by Staff-Surgeon Hanson are given below :—

Division 1.

None examined.

Division 2.

Case 513.—Optic discs, no papillary œdema. Vessels of right and left are more distended than normal but not tortuous. Superficial fibres of retina at edge of disc are greyer than usual and less distinct (? increased tension in subarachnoid fluid). No hyalitis. Nothing specific in arterioles of retina.

Case 986.—(A reinfection case. He had syphilis two years previously and had been cured.) Right vision $\frac{6}{6}$, D. 0·5. Left vision, less than $\frac{6}{6}$, D. 0·5. Slight hypermetropia. Orthophoria. No opacities in media. Fundi: Right eye : disc, fovea and vessels normal, but there are some streaks of greyish-white appearance between the superior retinal vessels which are not of recent origin. These streaks after a short separate course toward the right disc appear to coalesce at about $1\frac{1}{2}$ disc diameters from the disc. In right fundus also there are a few tiny areas of fatty degeneration about 0·5 mm. in diameter, approximately round. The retinal vessels are certainly not "plus." Immediately and completely and regularly around the right disc the retinal pigment is deficient over a zone 0·5 mm. wide. Left eye: disc, fovea and arterioles are normal. Venules are "plus." The grey streaks of right eye are here less obvious but still recognizable.

Case 1135.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Media clear. Fundi : Considerable pigmentation in excess in retina at periphery of right and left discs. The deeper portion of the retina shows tiny pale rounded areas (stippling). There is also an unusual amount of perivascular halo right and left.

Division 3.

Case 593.—No hyalitis. Discs right and left are a little hyperæmic and the surrounding retina is greyish in aspect. There is a trace left of perivascular lymph excess. No papillary œdema

Case 645.—There is retinal hyperæmia on the arterial side. Venules are normal. Discs and foveæ are normal.

Case 856.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Orthophoria. All details of discs are clearly seen, but there is some blurring at their temporal edges and in the adjacent superficial layer of the retina right and left. No general stippling. Vessels normal and symmetrical in size and contour.

Case 1119.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. D. 0·5. Colour perception normal. Fields normal. Orthophoria. Media and vitreous: clear right and left. Fundi: venules "plus." No enlargement of perivascular lymph sheaths noticeable. Stippling of right and left retina, especially in the periphery.

Case 1258.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Blurring of nasal disc margin. Cups clear at depth. No other changes noticed.

Division 4.

Case 139.—Right disc: Lower nasal margin of disc is a little blurred. Stippling and pigment disturbances of retina are present opposite this area. Vessels appear normal. Left eye: Pronounced physiological cup.

Case 251.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Media normal. Fundi: All details of discs clear. Following the arterioles and venules in their course there are areas in which their outlines become less clearly seen. There is stippling of the retinæ, and small pale cloudy areas in the deeper layers of right and left retinæ towards the periphery, of recent origin.

Case 555.—Some thickening of perivascular lymph sheaths of retinal vessels (right and left). Slight blurring of disc margin but no papillary œdema.

Case 560.—Left disc pale. Venules and perivascular lymph sheaths "plus." Right disc margin blurred; vessels over-full; perivascular lymph sheaths "plus."

Case 596.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Perivascular lymph spaces and venules "plus." Details of margins of right and left discs are not distinct. A clearing-up neuritis.

Case 598.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Discs right and left are hyperæmic; venules dilated and perivascular lymph sheaths near the disc are a little more pronounced than normal. No papillary œdema.

Case 690.—An unusual condition. Increased fulness and width of perivascular lymph sheaths of vessels.

Case 990.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. There is an increase in the perivascular lymph sheaths in right and left fundi. Nothing otherwise abnormal to be seen.

Case 1056.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Commencing stippling of right and left fundi peripherally. Veins a little "plus" and tortuous. No papillary œdema. No blurring of disc margin.

Division 5.

Case 384.—Right vision $\frac{6}{18}$. Left vision $\frac{6}{18}$. Hypermetropic astigmatism. With glasses: right vision $\frac{6}{6}$; left vision $\frac{6}{6}$. At extreme peripheries are to be seen post-retinitic changes in the deep retinal layers. Otherwise nothing abnormal detected.

Case 607.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Venules of right and left fundi are over-distended.

Case 652.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Stippling of left fundus near the papilla. Venules and lymph channels are "plus" in area immediately around the left papilla. Right eye: Nothing abnormal detected.

Case 840.—Blurring of details of elements of discs right and left. Left: stippling and thinning of choroido-retinal coat at temporal margins of disc. Venules and retina otherwise normal.

Case 1061.—Media, clear. Fundi: Some halo about the retinal area around the discs, vessels otherwise normal (? luetic halo). Fovea normal; fields normal.

Case 1274.—Distinct evidence of retinitis. Details of papillæ margins a little obscured.

Division 6.

Case 520.—Venules "plus" in left fundus.

Case 619.—White area in left disc extending half way around the marginal zone. Some fulness of perivascular lymph sheaths. Nothing else abnormal in fundi. Nineteen weeks later no change in fundi.

Case 792.—Vitreous, normal right and left. Both discs are a little hyperæmic, and their margins a little blurred with pigment disturbance in the deep layers of the retina. Venules: right normal in size, left "plus." No exudate; no papillary œdema; no stippling.

Case 829.—Fundi are both dark. No stippling. Right: areas of increased lymph sheaths, but venules normal. Left: the same, but sclerosis of retinal arterioles; the condition is not however symmetrical in extent.

Case 969.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Musculature and media: nothing abnormal detected. Right and left foveæ, papillæ and fundi, central and peripheral are normal. The superior retinal arterioles are tortuous and there is over-fulness of lymph sheaths round these vessels.

Case 1020.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Media normal. Fields and colour perception are normal. Fundi: discs normal but probably pale in contrast to the man's colour scheme represented in the eyes by deep pigmentation of retina and choroid. There is abnormal size and distribution of perivascular lymph sheaths and there are a few stipplings and rounded cloudy areas in the deeper layers of the retina, especially in the right eye, about four disc diameters in the first fork of the superior (retinal) temporal arterioles.

Case 1032.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. There is some indistinctness

about the nasal edge of left disc and the surrounding choroid. Venules are "plus"; otherwise nothing abnormal detected.

Case 1059. — (A reinfection case, having had syphilis three years previously.) Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Both papillæ are abnormal, especially the right, which shows traces of old papillitis not of recent origin. The vessels of the retina have an abnormal increase of perivascular lymph sheaths which is recent. Scattered over right and left fundi are tiny masses of pigment in the deeper layers of the retina and in places a few dots of fatty degeneration.

Case 1064.—Retinal venules are hyperæmic. Blurring of edges of discs.

Case 1084.—Details of both discs quite clear, but there is a halo in the retina around the discs, especially the right, probably indicative of old-standing changes in the lymph paths. A few of the arterioles also have this halo-like area, especially in the periphery. Some pigment cell degeneration in the retina but no marked stippling, choroiditic or post-choroido-retinitic atrophy.

Case 1142.—Chronic choroido-retinitis.

Case 1177. — Right vision $\frac{6}{24}$. Left vision $\frac{6}{9}$. Amblyopia and hypermetropic astigmatism. Musculature normal. Media, normal. Fundi, stippling; no increase of perivascular lymph sheaths; venules, "plus."

Case 1186.—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Both retinæ hyperæmic and venules "plus." Outlines of disc margins blurred, but details clear at depths of optic cups right and left. No peripheral retinitis.

Case 1281. — Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Media clear. There is some blurring of details at depth of right papilla; venules are "plus," but there is no exudate nor increase in perivascular lymph sheaths. Details of left papilla are almost undimmed, venules are "plus."

Case 1301—Right vision $\frac{6}{6}$. Left vision $\frac{6}{6}$. Media clear. Papillæ details clear. Finest twigs of arterioles show increased perivascular sheaths. Stippling of retina, especially in periphery right and left.

Case 1303.—Right vision $\frac{6}{12}$. Left vision $\frac{6}{6}$. Media, clear. Outlines of papillæ are seen distinctly except in right eye, where there is some exudate along the larger arterioles in the neighbourhood of papilla; venules not enlarged. Left fundus: one small patch of exudate above.

Case 1322.—Media, clear. Papillæ, normal. Stippling of retinæ. In both fundi there is marked increase in perivascular lymph sheaths.

(5) *A Comparison between the Findings from the Examination of the Cerebrospinal Fluid, Nervous System, Ears and Eyes.*

For convenience in comparison we append below a table of all abnormal cases in which at least one of the special examinations has been carried out. A list of all the cases described in detail is given on p. 300.

TABLE SHOWING THE VARIOUS FINDINGS IN EVERY CASE WITH AN ABNORMAL CEREBRO-SPINAL FLUID IN WHICH THE NERVOUS SYSTEM, EARS OR EYES WERE EXAMINED.

Division 1.

Case No.	Time between infection and examination	Cells per cubic millimetre in C.S.F.	Wassermann in C.S.F.	Symptoms of C.N.S. disease	Clinical signs of C.N.S. disease	Ears	Eyes
845	9 weeks	16	0	0	0	0	—
1241	8 ,,	10	0	0	0	0	—

Division 2.

513	14 weeks	84	2000	—	—	—	P
519	9 ,,	11	0	0	0	—	—
828	17 ,,	12	0	0	0	0	—
897	6 ,,	10	0	0	0	0	—
936	3 ,,	10	0	0	0	P	—
947	8 ,,	14	?	0	0	P	—
986	9 ,,	186	0000	0	0	0	P
1006	20 ,,	10	0	0	0	0	—
1009	4 ,,	36	0	0	0	0	—
1090	20 ,,	14	0	0	0	0	—
1135	20 ,,	476	0000	0	0	0	P
1163	22 ,,	10	0	0	0	0	—

Division 3.

593	11 weeks	742	4800	0	0	—	P
645	3 ,,	10	0	0	0	P	P
673	3 ,,	82	3000	—	—	—	0
734	9 ,,	57	0	0	0	—	0
765	10 ,,	24	0	0	0	P	—
770	10 ,,	14	0	0	0	0	—
821	4 ,,	10	0	0	0	P	—
831	11 ,,	10	0	0	0	0	—
856	4 ,,	50	0	0	0	0	P
874	3 ,,	28	0	0	0	0	—
1055	6 ,,	15	0	0	0	0	0
1119	9 ,,	22	0	—	—	—	P
1196	6 ,,	28	0	0	0	0	—
1214	8 ,,	10	0	0	0	0	—
1230	8 ,,	16	0	P	0	P	—
1258	5 ,,	36	4---	0	0	0	P

Division 4.

139	18 weeks	254	4---	P	0	0	P
251	22 ,,	362	4400	0	0	P	P
548	22 ,,	1000	4400	P	0	—	0
555	25 ,,	894	4000	P	0	—	P
560	16 ,,	834	4100	0	P	P	P
596	14 ,,	10	0	—	—	P	P
598	15 ,,	26	0	0	0	—	P
690	19 ,,	28	0	0	0	P	P
732	16 ,,	48	0	0	0	—	—
744	16 ,,	50	4---	0	0	P	—
780	13 ,,	14	0	0	0	0	—
783	18 ,,	23	0000	0	0	0	—
842	13 ,,	11	0	0	0	0	—
847	14 ,,	12	0	0	0	0	—
870	14 ,,	22	0	0	0	0	—
958	20 ,,	78	0	P	0	0	0
985	14 ,,	22	0000	0	0	—	—
990	22 ,,	80	0000	0	0	0	P
1017	21 ,,	44	0000	0	0	P	0
1021	20 ,,	12	0	0	0	0	—
1056	22 ,,	56	4400	P	P	P	P
1082	22 ,,	10	0	0	0	0	—
1098	22 ,,	140	1000	P	0	0	—
1331	?	34	0	0	0	0	0

TABLE SHOWING THE VARIOUS FINDINGS—*continued.*

Division 5.

Case No.	Time between infection and examination	Cells per cubic millimetre in C.S.F.	Wassermann in C.S.F.	Symptoms of C.N.S. disease	Clinical signs of C.N.S. disease	Ears	Eyes
88	11 years	0	4 - - -	—	—	P	—
384	9 ,,	144	4400	P	P	0	P
607	4½ ,,	38	0	P	0	—	P
652	30 weeks	72	4400	0	0	—	P
726	Denied	66	4400	0	0	—	—
781	7 months	34	0	0	0	0	—
840	25 years	42	0	P	P	0	P
878	15 months	20	0	0	0	P	—
930	18 ,,	22	0	0	0	0	—
956	22 years	10	0	P	0	0	—
1061	10 ,,	32	0	0	0	0	P
1071	7 months	164	0000	—	P	P	—
1274	15 years	200	4400	0	0	P	P

Division 6.

125	2½ years	1500	4 - - -	P	0	—	—
276	7 ,,	74	44 - -	0	0	0	—
279	11 months	26	1000	0	0	0	—
520	2 years	107	4440	0	0	P	P
619	9 months	156	4400	0	0	P	P
620	5 years	128	4400	0	0	—	—
627	4 ,,	14	4 - - -	P	0	P	0
664	21 months	11	0	0	0	0	—
695	14 years	48	?	0	0	—	—
705	9 months	38	4 - - -	0	0	—	—
713	17 ,,	28	Tube broken	0	0	—	—
753	14 ,,	184	0000	P	0	—	—
767	5 years	132	0	P	0	P	—
792	2½ ,,	380	4440	0	0	?	P
825	15 ,,	26	0	P	P	—	—
829	4 ,,	98	4400	0	0	P	P
907	2¾ ,,	50	0	0	0	0	—
957	18 months	10	0	0	0	0	—
969	?	38	4 - - -	0	0	0	P
1020	14 months	50	4000	0	0	0	P
1031	10 ,,	52	4100	0	0	P	0
1032	16 ,,	22	0	0	0	0	P
1059	?	42	4400	0	0	0	P
1064	Denied	16	0	P	—	0	P
1084	3 years	170	4400	P	0	P	P
1130	?	18	4 - - -	0	0	0	—
1137	11 years	92	4400	—	P	—	—
1141	14 ,,	104	4440	P	0	P	0
1142	10 ,,	100	4400	P	P	—	P
1164	7 months	1100	4410	0	0	P	0
1177	2 years	182	4400	0	0	0	P
1186	9 ,,	226	4444	—	—	—	P
1188	8 months	208	4000	0	0	P	0
1281	?	121	4 - - -	0	0	0	P
1301	2 years	20	0	0	0	P	P
1303	17 months	184	4400	0	0	P	P
1322	15 ,,	114	4400	0	0	P	P

TABLE SHOWING THE FINDINGS IN ALL "DOUBTFUL" CASES WHICH WERE EXAMINED.

Case No.	Time between infection and examination	Cells per cubic millimetre in C.S.F.	Wassermann in C.S.F.	Symptoms of C.N.S. disease	Clinical signs of C.N.S. disease	Ears	Eyes
			Division 1.				
1195	6 weeks	8	0	0	0	0	—
1219	8 ,,	8	0	0	0	P	—
			Division 2.				
838	11 weeks	8	0	0	0	—	—
935	8 ,,	9	0	0	0	0	—
1013	9 ,,	6	0	0	0	P	—
1014	16 ,,	5	0	0	0	0	—
1157	10 ,,	8	0	0	0	0	—
1261	6 ,,	8	0	0	0	P	—
			Division 3.				
771	11 weeks	8	0	P	0	0	—
827	11 ,,	6	0	0	0	0	—
1043	11 ,,	6	0	0	0	0	—
1238	9 ,,	8	0	0	0	P	—
			Division 4.				
335	24 weeks	8	0	0	0	0	—
590	22 ,,	8	0	0	0	—	—
701	17 ,,	8	0	0	0	—	—
934	14 ,,	6	0	0	0	0	—
1007	14 ,,	6	0	0	0	0	—
			Division 5.				
985	10 months	6	0	0	0	0	—
1297	4½ years	8	0	0	0	P	—
			Division 6.				
860	6 years	9	0	0	0	0	—
1175	7 months	8	0	0	0	0	—
1290	21 ,,	8	0	0	0	P	—

V.—THE EFFECT OF TREATMENT UPON THE ABNORMALITIES IN THE CENTRAL NERVOUS SYSTEM.

In fifty-four of the cases which exhibited "doubtful" or "certain" abnormalities in the central nervous system we have been able to repeat the examination of the cerebrospinal fluid on at least one occasion and sometimes more often. All had, of course, received treatment, but it must not necessarily be assumed that any change in the cerebrospinal fluid which is detected is consequent upon such treatment. The abnormalities in the nervous system are so much more common in the early stages of syphilis than are definite nervous manifestations in the later stages, that it must be admitted that many of the original abnormalities clear up more or less spontaneously.

TABLE SHOWING THE DETAILS OF CASES IN WHICH THE CEREBROSPINAL FLUID WAS RE-EXAMINED AFTER TREATMENT.

Case No.	BEFORE TREATMENT		Treatment between examinations	Interval (weeks) between first treatment and re-examination	AFTER TREATMENT		Division of disease
	Number of cells	Wassermann reaction			Number of cells	Wassermann reaction	
1219	8	0	3·6 grm. "914"	6	0	0	Division 1
1220	7	0	2·55 ,, ,,	7	4	0	
897	10	0	2·55 ,, ,,	6	0	0	Division 2
1006	10	0	2·05 ,, ,,	12	0	0	
1090	14	0	2·7 ,, ,,	12	24	0000	
1163	10	0	2·7 ,, ,,	5	2	0	
593	740	4300	4·5 ,, ,,	5	20	0	Division 3
			0·75 ,, ,,	9	2	0	
771	8	0	2·7 ,, ,,	7	4	0	
821	10	0	2·55 ,, ,,	14	4	0	
831	10	0	2·7 ,, ,,	8	28	0	
			2·7 ,, ,,	13	12	0	
856	50	0	2·55 ,, ,,	8	5	0	
1043	6	0	2·7 ,, ,,	8	20	0	
1119	22	0	2·7 ,, ,,	6	6	0	
1258	36	4---	2·7 ,, ,,	10	0	0	
139	254	4---	2·7 ,, ,,	8	14	3000	Division 4
355	8	0	2·7 ,, ,,	8	6	0	
548	1000	4400	4·5 ,, ,,	10	42	0	
			2·7 ,, ,,	23	3	0	
555	894	4000	4·5 ,, ,,	6	16	0	
560	834	4100	3·45 ,, ,,	5	70	0	
732	48	0	2·7 ,, ,,	8	2	0	
783	23	0	2·7 ,, ,,	7	2	0	
1007	6	0	2·7 ,, ,,	8	6	0	
				22	2	0	
1021	12	0	2·7 ,, ,,	9	2	0	
				17	9	0000	
1056	290	4---	2·95 ,, Galyl	4	56	4400	
			4·8 ,, "914"	10	22	4100	
384	144	4400	3·6 ,, ,,	5	68	4400	Division 5
			1·05 ,, ,,	14	20	-0--	
				21	28	4000	
607	38	0	2·7 ,, ,,	6	10	0	
			0·75 ,, ,,	24	10	0000	
726	66	4400	2·7 ,, ,,	7	10	4400	
				12	10	4400	
840	42	0	2·55 ,, ,,	10	8	0	
				24	6	0000	
876	5	0	2·4 ,, ,,	6	0	0	
927	16	0	4·45 ,, ,,	5	8	0	
956	10	0	2·55 ,, ,,	9	12	0	
1274	200	4400	2·7 ,, ,,	6	28	0	
1278	8	0	2·55 ,, ,,	13	8	0	
125	1500	4---	1·8 and				
			0·65 ,, "606"	56	18	----	Division 6
			3·45 ,, "914"	96	10	4300	
276	74	4400	2·7 ,, ,,	13	15	4000	
520	107	4440	4·5 ,, ,,	7	16	4---	
				16	10	0	
619	156	4400	3·3 ,, ,,	19	12	4000	
620	128	4400	2·25 ,, ,,	6	14	0	
627	14	4---	2·7 ,, ,,	8	2	0	
				11	2	0	
664	11	0	2·7 ,, ,,	8	2	0	
705	38	4---	2·7 ,, ,,	6	28	0	
				25	252	4400	

TABLE SHOWING THE DETAILS OF CASES—*continued.*

Case No.	BEFORE TREATMENT		Treatment between examinations	Interval (weeks) between first treatment and re-examination	AFTER TREATMENT		Division of disease
	Number of cells	Wassermann reaction			Number of cells	Wassermann reaction	
713	28	----		14	6	0	
740	112	4000	3·3 grm. "914"	6	10	3000	
			3·6 ,, ,,	14	10	3000	
753	184	0	1·8 ,, ,,	11	24	0	
767	132	0	3·15 ,, ,,	8	14	4---	
792	380	4440	2·7 ,, ,,	8	70	4400	
957	10	0	2·7 ,, ,,	10	4	0	
969	38	4---	2·7 ,, ,,	11	16	4---	
1084	170	44--	2·7 ,, ,,	8	26	4441	
1137	92	4400	2·4 ,, ,,	7	6	0	
1141	102	4440	2·4 ,, ,,	5	28	4400	
1164	1100	4410	4·65 ,, ,,	7	30	4000	
			? ,, ,,	10	0	3000	
1177	182	4400		7	8	4000	
			2·7 ,, ,,	13	4	0000	

Doubtful Cases.

Eight cases were examined with negative Wassermann reactions in the cerebrospinal fluids, but with cells numbering 5 to 9 per cubic millimetre inclusive. Of these, four became quite normal after treatment; three remained doubtful, while one (No. 1043 in Division 3) actually became definitely abnormal.

Case 1043.—Infected January 28, 1918. Examined April 17, 1918: Acquired phimosis, balanitis, subpreputial sores, marked general adenitis, papular syphilide; *S. pallida* found in penile sores, April 14, 1918; 6 L, W.R. 4/0, N. normal, B. abnormal, O. not examined, S. normal. He had six doses of 0·45 grm. "914" at intervals of three days from April 18 to May 7, 1918. Re-examined on June 13, 1918: 20 L., W.R. 0/0.

It is of interest to note that the disease in the general system was retrogressive as evidenced by the negative reaction in the serum, while the disease in the central nervous system was progressive.

Positive Cases.

Among the positive cases thirteen became quite normal. Most of these were only slightly affected at the beginning, but others had pronounced abnormalities; thus:—

Case 548.—Infected during the first week in September, 1917. Examined January 31, 1918: Scar of indurated sore in coronal sulcus; marked general adenitis; folliculo-papular syphilide; 940 L.+60 P., W.R. 4/4400, N. normal,

B. not examined, O. normal, S. positive (*vide* p. 281). Between January 31 and February 28, 1918, treated with 4·5 grm. "914" in nine doses. Re-examined on March 8: 42 L., W.R. -/0. From March 8 to March 18, 1918, given 2·7 grm. "914" in three doses. Re-examined June 4: 3L, W.R. 0/0. On January 31, 1918, *S. pallida* was found in the cerebrospinal fluid (*vide* p. 281).

Case 1177.—Infected in May, 1916. Had a sore on penis, treated with mercury injections for three months. Examined on May 7, 1918: Scars on glans, 182L., W.R. 4/4400; N. normal, S. normal, O. abnormal (*vide* p. 288) S. none. From May 8 to May 23 treated with 2·7 grm. "914" in six doses. Re-examined June 27, 1918: 8 L., W.R. -/4000. Again re-examined on August 8, 1918: 4 L., W.R. 4/0000.

The majority of the positive cases showed after treatment a marked diminution of the abnormal signs, although during the period of observation they had not become entirely normal.

Case 560.—Infected in October, 1917. Examined March 2, 1918: Scar of sore at frænum; general adenitis; mucous patches on tonsils and in mouth; condylomata ani; 834 L., W.R. 4/4100, N. abnormal (*vide* p. 282), B. abnormal, O. abnormal (*vide* p. 286), S. none. Treated with ten doses of "914," amounting to 4·95 grm., from February 2 to March 22, 1918. On March 9: 70 L., W.R. 0/0.

Case 619.—Infected in May, 1917. Originally had a sore on the penis. No treatment. Examined on February 9, 1918: Gonorrhœa; general adenitis; 156 L., W.R. 4/4400, N. normal, B. abnormal, O. abnormal (*vide* p. 287), S. none. Treated with seven doses of "914," comprising 3·3 grm. from February 9 to March 3, 1918. On June 18: 12 L., W.R. 4/4000. No change in the eye condition.

Case 792.—Infected in September, 1918. Had a sore on the scrotum and a secondary rash. In December and January, 1916-17, he was treated with 1·65 grm. of "914" and twenty-three injections of mercury. The W.R. was positive and became negative in March. In September, 1917, the W.R. relapsed and was also found positive in December, 1917. Examined on March 13, 1918: Scar of sore on scrotum; general adenitis; 380 L., W.R. 4/4440, N. normal, B. ?, O. abnormal (*vide* p. 287), S. none. Treated with 2·7 grm. "914" in six doses between March 13 and March 28. On May 9: 70 L., W.R. -/4400. Again treated with 2·7 grm. "914."

Three of the positive cases showed a definite increase in the abnormal signs after treatment:—

Case 1090.—Infected November, 1917. Said to have had a sore on the glans in January, 1918. Examined April 27, 1918: No scar: slight general adenitis; 14 L., W.R. 4/0, N. normal, B. normal, O. not examined, S. none. Treated with six doses of 0·45 grm. "914" between April 27 and May 13. On July 30, 1918: L. 24, W.R. 4/0.

Case 705.—Infected on April 6, 1917. Examined on April 25, 1917: Sore on glans; *S. pallida* positive. Treated with 1·65 grm. "914" in three doses from April 28 to May 22, 1917. In December, 1917, W.R. found to be positive and also on February 8, 1918. Re-examined on February 14, 1918: Multiple erosions on edge of prepuce and in sulcus; *S. pallida* not found; scars of sores on penis and scrotum; marked general adenitis; 38 L., W.R. 4/4---, N. normal, B. ?, O. not examined, S. none. Treated with 2·7 grm. "914" in six doses between February 14 and March 1, 1918. Re-examined April 3, 1918: 2 L., W.R. -/0. Again re-examined on August 15, 1918: 252 L., W.R. 4/4400. Treated with 2·55 grm. "914" in three doses between August 16 and September 3, 1918. Again re-examined on September 4, 1918: N., B., S., not examined, O. positive.

Case 831.—Infected December 24, 1917. Examined March 13, 1918: Acquired phimosis, subpreputial sores; *S. pallida* not looked for in view of local antiseptic applications; balanitis; general adenitis; papulo-squamous syphilide; gonorrhœa; 10 L., W.R. 4/0, N. normal, B. normal, O. not examined, S. none. Treated with 2·7 grm. "914" in six doses between March 14 and March 29, 1918. Re-examined May 10, 1918: 28 L., W.R. -/0. Treated with 2·7 grm. "914" in four doses between May 11 and May 26. Again re-examined on June 13, 1918: 12 L., W.R. 0/0. On September 13, 1918, he was recalled because the Wassermann reaction in the serum had become positive: On September 18, 1918: 262 L., W.R. 4/4400. No active lesions of syphilis apparent; N. normal, B. slightly diminished on both sides, O. not examined, S. none. He was given further treatment.

With regard to these three cases it will be seen that Case 1090 shows a continuation of the pathological process in the central nervous system in spite of treatment and a continuation of the positive Wassermann reaction in the serum. Case 705 is a case of early primary syphilis somewhat insufficiently treated. He was found later to have a positive Wassermann reaction in the serum and cerebrospinal fluid and numerous erosions on the penis. In view of the negative spirochæte test and the signs generally, it is probable that this indicates a relapse rather than a reinfection. The disease diminished on further treatment, but again relapsed more strongly and the man was then found to have a lesion of the eye. Case 831 illustrates a progression of the pathological process in spite of treatment, which later partially cleared up, and then relapsed to a much more abnormal condition than at the outset.

Negative Cases.

Cases which showed no abnormality at the first examination were not recalled, and therefore we have no evidence that such cases may develop a lesion of the central nervous system after treatment. We

have not yet observed an instance of "nerve relapse" in any case in which the central nervous system was originally found to be normal, but such may of course occur later as an accompaniment of a general relapse.

VI.—The Relation of the Wassermann Reaction in the Serum to the Condition of the Central Nervous System.

It is of some practical importance to determine whether:—

(1) A negative reaction in the serum excludes a pathological process in the central nervous system.

(2) A persistent positive reaction in the serum indicates a pathological process in the central nervous system.

(1) This question has to be considered from two different points of view, depending upon whether the case is untreated or treated.

Untreated cases of syphilis show in practically every instance a positive reaction in the serum, except when they are observed in the early primary stage. Therefore the only cases which throw light upon the subject under discussion are the Division 1 cases in which the reaction is negative. There are eleven instances of abnormality in Division 1 in our series. In nine the cases were "doubtful," while in two (Cases 845 and 1241) they were abnormal, namely, 10 and 16 cells per cubic millimetre.

It may therefore be held that these two cases of primary syphilis with a negative reaction in the serum have nevertheless a pathological process in the central nervous system.

With regard to *treated* cases, it is and has been well known that certain syphilitic lesions of the central nervous system may develop as a relapse while the serum is still negative. Such lesions are usually affections of the cranial nerves. Anti-syphilitic treatment has undoubtedly a more effective action upon syphilitic disease in the general system, of which the serum reaction is an indicator, than in the cerebrospinal system, and thus spirochætes may be left to relapse in the latter when the former has been sterilized. This is undoubtedly the explanation of the occurrence of relapses in the central nervous system when the serum reaction is negative.

We have observed two instances of this phenomenon in the whole of the present series:—

Case 907.—Infected August 4, 1915. He had gonorrhœa and a sore on the penis. He was treated with one dose of "606" in October, 1915,

followed by Hg pills for six months. On March 13, 1918, he was given one dose of galyl. He was examined by us on March 23, and no lesions were present except marked general adenitis. 50 L., W.R. 0/0, N. 0, B. 0, O. not examined, S. none. He was treated with 2·7 grm. "914" from March 24 to April 8. On August 23 the Wassermann reaction in the serum was also negative.

This man, therefore, had a syphilitic meningitis (50 cells) associated with a negative reaction in the serum.

Case 1071.—Infected September 1, 1917. Sore on penis which apparently remained untreated. It healed up and broke down again in January, 1918. *S. pallida* positive. Treated with 0·75 grm. galyl during January and February. Examined by us on April 20, 1918: Facial paralysis and deafness on the left side had developed on April 4; general adenitis; complete facial paralysis and internal ear deafness; 164 L., W.R. 0/0000, N. abnormal (*vide* p. 282), B. diminished on both sides, right > left, O. not examined, S. (*vide* p. 282). Refused more than four doses of "914." On May 5 the W.R. was positive in the serum.

This is a typical instance of a "nerve relapse" associated at first with a negative reaction which later became positive.

Similarly a progressive disease may be present in the central nervous system without producing symptoms, while the serum is found momentarily negative as the result of treatment. Such an example is to be found in Case 1043 described on p. 293. Thus it must be admitted that the fact of a negative reaction in the serum does not exclude a progressive nervous disease, whether the case has been treated or not. Nevertheless it may be said to render the existence of such a nervous disease improbable, but, in view of the importance of early treatment in such cases, it is doubtful whether it is justifiable to withhold the proof of lumbar puncture in any instance. This is of course especially important whenever the central nervous system has been shown already to have been affected previously.

(2) When the Wassermann reaction persists in a positive condition beyond the period when it should normally become negative as the result of treatment, it is to be assumed that a refractory focus of disease exists in the body, and this refractory focus may be in the central nervous system. Our results give some indication that this assumption is often correct. In twenty-six of the cases in which the central nervous system was abnormal and in which repeated examinations of the serum and cerebrospinal fluid were made, no less than fourteen still showed a positive reaction in the serum, when in a "normal" case

it would be expected to be negative. This is a higher proportion than would ordinarily be found in a series of cases with unaffected cerebrospinal systems, and therefore it may be assumed that a positive reaction which persists to an abnormal extent is suggestive of disease in the cerebrospinal system, and is thus an indication for immediate lumbar puncture.

VII.—Conclusions.

In drawing conclusions from the preceding work, we consider it undesirable to discuss any hypothetical questions relating to the connection between these early conditions and the later manifest signs of syphilis in the central nervous system. We propose to confine ourselves to the facts which we have observed.

We have examined 624 syphilitic men, of whom the great majority were in the early stages of the disease and showed no obvious signs of nervous disease. Of these, 18 per cent. showed undoubted signs of an abnormal condition of the central nervous system (p. 271). Thus we are able to confirm the work of earlier writers, although the number of abnormal cases is considerably less in our series than in those of some others. This is partly due to the fact that cases which we have described as "doubtful" are not included in this estimate. If, as we consider justifiably, these also are looked upon as abnormal, the percentage of affected men reaches 30.

Even this figure is not so high as some found in the literature, and it should be understood at once that statements of the numbers of men affected are totally devoid of significance, unless accompanied by an indication of the *stage of the disease*. We have found that there is a pronounced difference in the incidence of abnormal conditions at different stages of infection (p. 271). There is a progressive increase of these up to the secondary stage (Division 4), but a slight decline in the later manifest secondary and tertiary period (Division 5). In the case of those men, however, in Division 6 who show no symptoms (namely, the so-called latent stage) there is a pronounced increase in the number affected. In our series, of all men who have been affected for more than six months and showed no symptoms, no less than 35 per cent. had abnormal central nervous systems.

If the number of men found to be abnormal by us is less than appears from the work of some other authors, this is adequately explained by the fact that our series includes a large number of men in the first weeks of the disease (p. 272). The onset of the abnormality

may be very early. It was even demonstrable in two cases before the Wassermann reaction had become positive in the serum after infection (p. 272). The nature of this abnormality in the central nervous system does not admit of doubt. It is a syphilitic meningitis. We found this opinion not only upon the presence of lymphocytes in the cerebrospinal fluid but also upon the frequent appearance of polymorphonuclear leucocytes in the more pronounced cases. Furthermore, in a large proportion of the abnormal cases, the fluid showed a positive Wassermann reaction (p. 276), while in one case we even found *S. pallida* by the method of dark-ground illumination (p. 280).

There is no evidence that previous arsenical treatment increases either the number or severity of the affected cases (p. 274).

An outstanding feature of these cases is the almost total lack of symptoms. Very few of the men complained of any disability (p. 281) even when the meningitis was acute enough to produce a visible opalescence in the cerebrospinal fluid.

Very few of these men showed any clinical signs of nervous disease detectible by our examination (p. 281). On the other hand a considerable proportion of the abnormal cases had lesions of the eye grounds, which were indeed of slight extent, but which, nevertheless, indicated a commencing retinitis (p. 284).

A certain number of cases showed affections of the internal ears, but there was no evidence that these were commoner than among non-syphilitics or syphilitics with apparently intact nervous systems (p. 283).

Antisyphilitic treatment has a marked ameliorating action upon these conditions. Some are rapidly reduced to normal, while the great majority were shown to be improved within the period of observation (p. 291). On the other hand, a few of the cases showed a remarkable resistance to treatment, indeed the meningitis actually progressed in spite of repeatedly renewed treatment (p. 294).

Although the demonstration of a negative Wassermann reaction in the serum denotes that an affection of the central nervous system is improbable, nevertheless it does not exclude it (p. 296), and in view of the importance of early treatment (and the value of the operation in prognosis) it is probable that lumbar puncture should never be omitted as a routine in the examination of all cases of syphilis.

VIII.—References to Cases quoted.

The following cases are described in detail on the pages mentioned :—

Case	88	..	on page 280	Case	907	..	on page 296
,,	251	..	,, 273	,,	986	..	,, 273
,,	513	..	,, 276	,,	1043	..	,, 293
,,	520	..	,, 278	,,	1059	..	,, 277
,,	548	..	,, 293	,,	1071	..	,, 297
,,	555	..	,, 273	,,	1090	..	,, 294
,,	560	..	,, 294	,,	1130	..	,, 277
,,	593	..	,, 278	,,	1135	..	,, 280
,,	619	..	,, 294	,,	1164	..	,, 274
,,	673	..	,, 278	,,	1175	..	,, 274
,,	705	..	,, 295	,,	1177	..	,, 294
,,	740	..	,, 278	,,	1195	..	,, 272
,,	771	..	,, 282	,,	1230	..	,, 273
,,	792	..	,, 294	,,	1238	..	,, 273
,,	825	..	,, 274	,,	1258	..	,, 278
,,	829	..	,, 278	,,	1274	..	,, 273
,,	831	..	,, 295	,,	1281	..	,, 277
,,	838	..	,, 273	,,	1297	..	,, 274
,,	845	..	,, 272				

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THE EXISTENCE OF TWO DISTINCT PHYSIOLOGICAL SYSTEMS FOR THE TRANSMISSION OF MOTOR IMPULSES IN PERIPHERAL NERVES.

[A PALEO-KINETIC SYSTEM SUBSERVING THE FUNCTION OF AUTOMATIC AND ASSOCIATED MOVEMENTS; AND A NEO-KINETIC SYSTEM FOR ISOLATED SYNERGIC MOVEMENTS OF CORTICAL ORIGIN.][1]

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CHAPTER I.—INTRODUCTION.

THE problem of motility, notwithstanding the many notable contributions of recent years, is far from a final solution. This is true of reflex action, associated movement, hypertonicity after central lesions, and cerebellar function. It is especially true of all that pertains to the extra-pyramidal motor pathways.

The present study is a preliminary statement of certain views which I hold in regard to these questions.

Some of my conclusions are founded upon clinical evidence only, while others rest upon a firm anatomical basis. Some are merely speculative and of a theoretical nature. Together they constitute a conception of the neural pathways underlying motility which may help to clarify much that is obscure in this important field.

At this time it is not possible for me to pursue my investigations further. My presentation, therefore, is suggestive rather than complete. As the subject, however, is closely related to certain aspects of the neurology of war, this outline of my views is offered in the hope that it may be of service to other students in this field.

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In our conception of motility as it relates to the peripheral nervous system, we think of motor nerves as subserving a single function only, the transmission of motor impulses from the anterior horn-cells of the spinal cord to the skeletal muscles. This is the conception of the final common path as enunciated by Sherrington, in which all varieties of motor impulses converging from the various central pathways are supposed to traverse a single physiological system of peripheral motor neurones.

The present study is a consideration of evidence from various sources which would appear to suggest a modification of this view, to the extent of recognizing two great physiological systems for the transmission of motor impulses in peripheral nerves, corresponding to certain cardinal differences in the nature of movements and their relation to special integrative and correlating centres in the central nervous system.

If motility is resolved into its component parts three fundamental types of movement may be recognized corresponding to important stages in the phyletic development of the nervous system.

There are, for example, reflex movements which are very primitive and correspond to different levels of the segmental nervous system; there are automatic and associated movements which are under the control of certain infra-cortical centres, and there are isolated synergic movements of cortical origin. The isolated synergic movement is the highest type of motility yet produced in the course of evolution of the central nervous system, and finds its most complete expression in man.

The motor impulses of cortical origin pass over a special system of fibres known as the pyramidal tracts, the existence of which has been established by evidence from many sources. One of the most striking proofs of the existence of such a system has been furnished by the developmental method which shows this system to be of comparatively recent origin in the phylogenetic sense, and one of the last of the great neurone systems to receive its myelin sheath.

At birth the pyramidal tracts are still shorn of their myelin sheaths, which develop gradually during the early years of infancy. Van Gehuchten [20] called attention to the interesting fact that even as late as the eighth month of fœtal life the pyramidal tracts in the spinal cord contain no axis cylinders which have not descended below the decussation of the pyramids in the medulla oblongata.

It is therefore evident that other tracts in the spinal cord must also

subserve a motor function, as an infant born prematurely at the seventh month displays an extraordinary power and diversity of movement.

There must therefore exist in the cerebrospinal axis other groups of fibres subserving the function of motility, and these are now generally recognized as the extra-pyramidal motor system. In this system the rubro-spinal tract of Monakow is perhaps the best known and most important, arising in the red nucleus and traversing the entire length of the spinal cord. Abundant evidence has also been furnished from other sources—clinical, pathological, experimental and comparative—showing the existence of extrapyramidal motor tracts in the central nervous system; and that these are of especial importance in the lower forms of life where cortical development is rudimentary.

In previous studies I have presented evidence which would appear to indicate that the extrapyramidal motor system is under the control of the corpus striatum and that a loss of the large motor cells of the corpus striatum in man is associated with the clinical phenomena of paralysis agitans. Paralysis agitans, according to this conception, is produced by a break in the strio-spinal system of motility and is the counterpart in the extrapyramidal system of spastic paralysis following lesions of the pyramidal tracts.

In paralysis agitans there is a progressive loss of certain automatic and associated movements, in contrast to spastic paralysis where the isolated synergic movements of cortical origin are abolished. These two systems are therefore anatomically and physiologically distinct, each contributing in its own way to the normal harmony of movement.

The strio-spinal system is the older and more primitive mechanism and the homologue in man of the basal fore-brain bundle and the primary motor fasciculus of the lower forms of life. Automatic and associated movements must therefore be phylogenetically older than the isolated synergic movements of cortical origin, just as reflex movements must have antedated the appearance of automatic and associated movements.

Typical reflex movements are therefore purely spinal and the first to appear in the evolution of animal life. Next in order would come the various automatic and associated movements which would correspond to the development of a primitive correlating mechanism, the corpus striatum. The most recent addition to motility is the isolated synergic movement of cortical origin which permits of the special dissociations underlying the various skeletal acts which have contributed so largely to the progress of man.

Each of these fundamental types of movement is represented and plays an important rôle in motility—all are united and fused by the integrative action of the nervous system. These various mechanisms may, however, be unmasked by the accidents of disease, which allow us to retrace the various evolutionary steps of differentiation and integration of the nervous system.

In the present study evidence is presented which would appear to indicate the existence of a similar physiological division of motor systems in peripheral nerves; one of these is for the transmission of automatic and associated movements, which because of its age and more primitive function may be termed the paleo-kinetic system. The other is for the transmission of isolated synergic movements of cortical origin, and may be distinguished as the neo-kinetic system.

The paleo-kinetic function represents a more primitive and more diffuse form of movement, which is under the control of the corpus striatum and is subserved by a strio-spino-neural system. The neo-kinetic function is a more highly specialized form of movement which is under the control of the cerebral cortex and is subserved by a cortico-spino-neural system.

According to this conception the skeletal musculature which is the peripheral organ of motility is innervated by two distinct systems of fibres which are physiologically and anatomically distinct: A paleo-kinetic system for automatic and associated movements and a neo-kinetic system for the isolated synergic movements of cortical origin.

With this differentiation in the central and peripheral motor system, which represents two distinct phases in the evolutionary development of motility, there is, I believe, a corresponding differentiation of reflex function, so that it will be possible to recognize certain paleo-kinetic and neo-kinetic reflex manifestations referable to one or the other of these two systems.

It is not without interest to recall that Henry Head [6] and his collaborators in their exhaustive study of the afferent nervous system have reached somewhat similar conclusions.

They find evidence in the peripheral nervous system of the existence of two distinct types of sensibility, a protopathic and an epicritic. The protopathic is a lower order of sensation in contrast to the epicritic sensibility which finds its interpretation in the cerebral cortex.

The diffuse primitive character of the protopathic sensibility suggests a certain analogy to the diffuse contractions of automatic and associated movements. On the other hand, the discriminative quality

of the epicritic sensibility is in the sensory sphere the counterpart of the isolated synergic movement of cortical origin.

It is also significant that the optic thalamus, which is the great infracortical station for protopathic sensibility, stands at the same physiological level as the corpus striatum which, according to my conception, is the organ for control of automatic and associated movement.

There is accordingly a certain harmony in the conception of the afferent nervous system as enunciated by Henry Head and that of the efferent systems which I shall endeavour to present in the following pages. According to both hypotheses there exists a more primitive system subserving an ancient function which is related to the basal ganglia in addition to a more highly specialized system of cortical origin.

Chapter II.—The Restoration of Motor Function after Injury to Peripheral Nerves.

Peripheral nerves in contrast to the central nerve tracts may under suitable conditions regenerate after injury, with more or less complete restoration of function. This regenerative capacity is probably closely related to the existence of a special sheath termed the neurilemma. Generally speaking, sensory function is restored before motor function and if the hypothesis of Henry Head is accepted the primitive or protopathic type of sensibility precedes the return of the more highly specialized epicritic sensation.

There is, however, clinical evidence to show that in the restoration of motor function after injury a certain differentiation of function is also possible and that motility of a more primitive type as represented by automatic and associated movements makes its appearance before the return of the dissociated synergic movements of cortical origin. Thus there is a certain parallelism in the functional restoration of both motor and sensory nerves which appears to be dependent upon the existence of nerve fibres presenting different degrees of vulnerability and specialization.

It has been noted by a number of observers that after injuries of peripheral nerves there is a return of muscle tonus and a diminution of the atrophy long before voluntary movements are in evidence.

Tinel [19] in his treatise on the Injuries of Nerves states that the sequence of events in the regeneration of motor nerves is as follows:

(1) "The first evidence of beginning restoration of function is the return of muscle tone. The muscle develops a firmer consistence and there is a progressive modification of the paralytic posture of the limb. Atrophy also diminishes.

(2) Soon there is a return of muscle sensibility.

(3) The return of voluntary movement is the latest "manifestation of regeneration. It first shows itself by a slight hardening of the muscles which accompanies the efforts of the patient, and particularly the energetic contraction of the antagonistic muscles; no movement, however, is apparent."

"Then there appear faint voluntary movements necessitating considerable effort on the part of the patient and bringing into play the violent synergic contraction of all the muscles of the limb. Finally, the movement becomes definite, but they long remain weak, clumsy and quickly exhausted, evidencing rapid fatigue accompanied by slight trembling."

In this description, which is based on a large experience with gunshot injuries of nerves, it would appear that the earliest evidences of motility in the paralysed distribution are associated with forcible contraction of all the muscles of the limb, viz., associated movements, and that only later do the movements become dissociated and then are feeble and readily exhausted for a considerable period.

Not long since, while serving on a Medical Advisory Board in connection with the draft, there was referred to me the following rather curious case:—

The man was thirty years of age and worked in a tailoring establishment. Fifteen years previously, his right upper arm had been severely gashed in the middle of its posterior aspect by a circular saw in such a manner as to involve the musculospiral nerve. He was taken to a hospital, where the hæmorrhage was checked and the wound sutured. The injury was followed by immediate and complete paralysis in the distribution of the musculospiral nerve. As there was no improvement in the motor function after a year of conservative treatment a secondary operation was performed, and an attempt was made to suture the divided nerve. This operation was performed in Russia and it was impossible to ascertain the condition in which the nerve was found, or the success of the operative procedure.

In the course of time there had taken place a certain improvement in function, but he had never entirely regained the function of the paralysed muscles and the usefulness of the hand was seriously impaired

At the time of my examination, which was fifteen years after the original injury and fourteen years subsequent to the attempted nerve suture, the clinical picture was as follows: There was a ragged scar on the middle of the posterior aspect of the right upper arm which had evidently extended through the muscle mass of the triceps to the bone. In addition, there was the scar of a longitudinal incision on the posterior aspect of the arm in the course of the musculospiral nerve, which coincided with the site of the previous operation.

There was complete paralysis of the supinator longus, and the extensors of the wrist, thumb and fingers for all movements of cortical origin. When the forearm was held out with the hand open, there was the typical position of wrist-drop. Flexion of the elbow-joint produced not the slightest evidence of contraction of the supinator longus. Attempts to extend the thumb, fingers or wrist evoked no corresponding movement of the parts. There was, therefore, a total paralysis for all isolated synergic movements of cortical origin in the distribution of the musculospiral nerve.

When, however, the hand was closed tightly, as in making a fist, all the muscles of the forearm and upper arm were immediately thrown into strong, firm contractions. The supinator longus contracted firmly, and stood out prominently; the extensor muscles on the back of the forearm were felt to contract forcibly and the hand no longer dropped but assumed a position of extension. In this position, palpation showed the long extensors of the thumb and fingers and the extensors of the wrist to be exerting firm contractions.

In other words, muscles which failed to respond to a willed movement of cortical origin were thrown into active contractions when another type of movement was initiated—the grasping movement of the fist belonging to the type of automatic and associated movement in contrast to the isolated extension of the wrist and fingers which is of cortical origin.

On opening the hand, the extensors immediately relaxed, the hand dropped and the attitude and characteristic deformity of musculospiral palsy were again evident.

Sensation, so far as I was able to determine by routine clinical tests, was not affected in the distribution of the radial nerve. The response was prompt to light touch with cotton wool; to pin prick and to heat and cold over the hand and forearm, both anteriorly and posteriorly.

The sense of localization was also present. Pressure over the

extensor muscles of the forearm evoked a distinct sensation of pain similar in character and intensity to that of the unaffected side. The sense of posture in the fingers was also intact. If, therefore, a slight disturbance of sensibility was still present it was not detected by usual sensory tests.

On electrical examination, the extensor muscles of the forearm, including the supinator longus, responded promptly to the direct application of both faradic and galvanic currents. There was no sluggishness of the responses and no qualitative changes or reversal of the formula.

I was unable, however, to elicit isolated contractions in the musculospiral distribution with either current on application of the electrode above the site of the injury. Strong currents evoked a general diffuse contraction of all the muscles of the forearm, which was present in the extensors and was especially active in the flexor group.

It was, however, impossible to pick out the musculo-spiral nerve with the electrode and induce the typical extensor movements of the hand and fingers.

How is this curious dissociation of motor activities to be explained? Here was an old injury of the musculospiral nerve in which there was no return of the isolated movements of cortical origin, as, for example, the participation of the supinator longus in flexion of the elbow or the isolated movements of extension of the wrist, thumb and fingers, and yet all of these same muscles would undergo strong contractions on making a fist.

Phylogenetically, the grasping movement of the hand is an older type of movement and is probably closely related to the climbing period of our ancestry. It is, for example, readily demonstrable in the infant before the pyramidal tracts are fully developed. A strong grasping movement of the hands may be observed in infants born prematurely at the seventh month, at which period the axis cylinders of the pyramidal tracts, according to Van Gehuchten, have not yet descended below the decussation and therefore could not be functionating in the spinal cord.

It is therefore reasonable to infer that the various movements of the infant born at the seventh month pass over some motor system other than the pyramidal tract and this mechanism is represented according to my conception by the striospinal system, viz., the corpus striatum and the extra-pyramidal motor tracts. This being an older mechanism for the control of automatic and associated movements, it antedates phylogenetically the corticospinal system: A fact which is

corroborated by myelinization studies which show that the ansa system and the antero-lateral ground bundles of the spinal cord receive their myelin sheaths as early as the fifth month of fœtal life.

It would therefore appear that we have in this case of old musculo-spiral palsy a peripheral motor system which is capable of transmitting impulses from the striospinal mechanism, but none for the transmission of the higher and more specialized types of movement of cortical origin.

The injury to the nerve trunk must have been of such a character as to prevent effectually the regeneration of the more highly specialized fibres subserving a cortical function, but owing to the more primitive character of the other motor system regeneration and restoration of function was possible.

Any anatomical differences between these two systems are as yet purely conjectural. The clinical evidence, however, would suggest that the more primitive function is subserved by a lower order of nerve-fibre, possibly non-medullated or very finely medullated nerve-fibres which sprout from the central end of the divided nerve and invade the adjacent parts. Such fibres may bridge a large gap and wander through dense fibrous deposits to reach the distal end of the nerve, and thus subserve the function of primitive motility. Perhaps frequent division of the nerve-fibres may also play a rôle.

Ramon y Cajal [15] and others have shown in studies on the regeneration of nerves that innumerable non-medullated fibres grow out from the central stump and invade the surrounding tissues—many of these fibres undergoing division. It is therefore possible that primitive types of diffuse associated movements are subserved by fibres of this type which are capable of passing through obstructions which would be insuperable to the more highly specialized nerve-fibres subserving a cortical function.

Regeneration studies would appear therefore to favour the idea that the medullary sheath is a factor in the differentiation and specialization of nerve function which permits of the more isolated and dissociated types of cortical movement.

In another patient, a young woman who had suffered a severe compression paralysis of the musculo-spiral nerve, a similar dissociation of motility was observed with return of function. When she first came under my observation, two weeks after the injury, there was complete paralysis of the musculo-spiral nerve, including the supinator longus, the extensors of the wrist, thumb and fingers. The extensor muscles of the forearm were in a state of complete relaxation with typical wrist-

drop. There was also anæsthesia to touch, pain and temperature in the radial distribution of the nerve. The muscles showed complete reaction of degeneration. Three months later sensation was practically restored save for paræsthesia and slight impairment of tactile sensibility and localization in the radial distribution. There was, however, no return of power on attempting to carry out isolated movements in the paralysed muscles. Forced flexion of the elbow produced no contraction of the supinator longus, and strong efforts to extend the wrist, thumb, or fingers were of no avail. There was still complete paralysis for isolated synergic movements of cortical origin in the paralysed distribution. When, however, the hand was closed tightly in a grasping movement, as in making a fist, distinct evidence of muscular contractions were palpable both in the supinator longus and the long extensors of the wrist, thumb, and fingers. There was also evident return of muscle tone in the paralysed muscle. The reactions of degeneration were still present.

Here, again, were encountered evidences of a dissociation of motility during the period of restoration of function after injury. There was absolutely no sign of an isolated movement of cortical origin in the paralysed distribution, and yet very evident signs of contraction were produced by a more primitive type of associated movement. This would appear to indicate either a lessened vulnerability of the older system or a more rapid regenerative capacity after injury.

A somewhat similar observation was recorded some years ago by Oppenheim [14]. A 7-year-old girl had a pressure paralysis of the left musculo-spiral nerve of nine weeks' duration. There was wrist-drop and complete paralysis of all the muscles supplied by the musculo-spiral nerve for all forms of voluntary movement. It was noted, however, that when the fingers were tightly closed, as in grasping an object, the hand was thrown into hyperextension. It was also observed that during certain purely automatic acts the hands and fingers were extended. That it was a case of true peripheral palsy was shown by presence of the reactions of degeneration.

Oppenheim attempted an explanation of the phenomena by assuming a loss of cortical memories for movement, a habit paralysis (Gewohnheitslähmung), as this term was used by Huet [7]. He thought that this factor may have been enhanced by the mental condition of the child, who was both imbecile and epileptic. Later, under appropriate electrical treatment, the paralysis cleared up, and cortical movements were completely restored.

The explanation which was offered by Oppenheim, while suggestive, is far from satisfying. It seems hardly possible that cortical memories could have been so completely obliterated after so short a period of time, and why, might one not inquire, is the condition not more frequently encountered after palsies of the peripheral nerves?

It is my belief that the phenomena may be more satisfactorily interpreted by the assumption of the existence of two distinct physiological systems for the transmission of motor impulses in peripheral nerves, and that the paleo-kinetic system is not only less vulnerable, but regenerates more readily after injury. Such a conception would appear to explain quite naturally the early return of automatic and associated movements, which are diffuse and primitive in their nature, while the more highly specialized function of cortical origin would require a longer period for recovery because of the more delicate differentiation of the nerve-fibres subserving the neo-kinetic function.

A somewhat similar manifestation was described by Jacobi as early as 1877, and finds frequent mention in the literature.

Jacobi [12] had suffered in his own person a serious injury of both the musculospiral and median nerves. After recovery he found that it was quite impossible to contract isolated muscle groups, but only all of them together. In other words, diffuse associated contractions were present in the paralysed muscles without, however, the power of isolated movements.

Here, again, in an old lesion of peripheral nerves the strio-spino-neural pathway (paleo-kinetic system) was open, while the cortico-spino-neural pathway (neo-kinetic system) was broken and would not convey impulses from the cerebral cortex to the muscles.

I have also observed a similar dissociation of motility after an old injury of the median nerve, and in a case of old gunshot wound of the external popliteal nerve. In both cases there were distinct evidences of a return of associated movement in the paralysed muscles without the power of isolated movement in the corresponding neural distribution. A return of protopathic sensibility was demonstrable; while the epicritic sensibility was still absent. The paralysed muscles possessed some sense of pain on deep pressure. Electrical examination showed complete reaction of degeneration.

In both cases, exploratory operation revealed serious injury of the nerve trunks, which were embedded in a mass of sclerotic cicatricial tissue.

In these cases, although several years had elapsed since the injury,

regeneration of the more highly specialized neo-kinetic system had not taken place and yet paleo-kinetic movements were evidently present, which harmonizes in the sensory sphere with the return of protopathic and the absence of epicritic sensibility. This would therefore appear to confirm my theory that those fibres subserving the more primitive functions of motility traverse with greater ease gaps and sclerotic obstructions than is possible for the more highly differentiated fibres conveying cortical impulses.

The Restoration of Motility after Facial Palsy.

By reason of its rich and comparatively superficial distribution and the character of the muscles innervated, the facial nerve offers peculiar advantages for the study of motor function.

The facial musculature in addition to voluntary movements of cortical origin presents a wide range of movement of another kind, which is concerned with the expression of the emotions. These are essentially of the automatic and associated type.

The centre for the emotional innervation of the face was long held to be localized in the anterior portion of the optic thalamus, following the teachings of Nothnagel and Bechterew.

In previous contributions to the functions of the corpus striatum [8 and 9] I have presented evidence for the assumption that the essential mechanism for the control of the emotional innervation of the face is centred in the corpus striatum and that facial expression is a part of that large system of automatic and associated movements which is under the control of the striatal mechanism.

In paralysis agitans, for example, which is the extreme expression of a loss of the essential motor mechanism of the corpus striatum, a loss of the emotional innervation of the face is one of the most striking symptoms, the Parkinsonian mask.

In such cases, while the face is motionless so far as expression is concerned, there is nevertheless retained the power of cortical innervation (isolated movements) which are simply impaired by the increased tonicity of the musculature. So far, therefore, as facial motility is concerned, there are two great types of movement which may be dissociated by organic disease of the central nervous system : a lesion of the cortico-spinal system (pyramidal tracts), producing spasticity and loss of isolated movement, as in spastic palsies ; a lesion of the strio-spinal system (pallidal system) producing rigidity and loss

of the automatic and associated movements subserving the function of expression as in paralysis agitans.

The facial muscles have, therefore, a dual function physiologically distinct, and according to my conception this duality of function is subserved peripherally by two distinct systems of nerve-fibres: a strio-neural or paleo-kinetic, and a cortico-neural or neo-kinetic system.

If the restoration of motor function after facial palsy is carefully observed, I think that many facts confirmatory of this point of view will be found.

For example, the first movement to return in cases of facial paralysis is a closure of the eyelid, associated later with a slight contraction of the muscles about the angle of the mouth. This associated movement of the angle of the mouth on closure of the eye becomes more pronounced as improvement continues and antedates often for a considerable time the ability to contract by isolated movement of cortical origin this same region of the face.

Subsequently, as function is restored, other movements of the associated type appear, and more especially in those severe cases in which voluntary activity is long delayed or perhaps permanently affected.

In such cases the affected side becomes contracted by a more or less continual spasm, which, however, is increased and exaggerated by the natural emotional play of the facial muscles in talking, laughing and crying.

Where these conditions obtain it would seem as if the older paleo-kinetic system showed greater powers of regeneration than the more highly specialized neo-kinetic system; hence the diffuse contractural states, hypertonicity and multiplicity of associated movements after old facial palsies.

An interesting case of old facial palsy is cited by Ballance and Stewart [1] in which a contractural condition had developed on the paralysed side, without the power of voluntary movement.

Following an operation for nerve anastomosis, the contractural state disappeared, although the nerve was found completely divided and disconnected, showing that there had been a certain power of innervation, although apparently a complete separation of the divided nerve had taken place.

In the discussion of this case, Ballance says: "This is a condition for which we do not offer any explanation, except possibly in such cases

the nerves, though completely disconnected from the brain, do in some way by virtue of the regeneration that has taken place in them exert an influence on the muscles."

According to my conception, such a case would be explained by the passage of a lower order of nerve-fibre of the paleo-kinetic system through the tissues, bridging gaps and overcoming obstructions and eventually reaching the distal portion of the nerve. This regeneration if more primitive would permit a return of muscle tonus and certain automatic and associated movements, the severe nature of the lesion precluding a regeneration of the fibres of the more highly specialized neo-kinetic system. In such an event, the anastomosis operation would naturally have destroyed that small portion of the paleo-kinetic motility which had been restored.

It is perhaps also significant that after cases of nerve anastomosis in which the hypoglossal or spinal accessory nerves have been united with the distal stump of the facial, the emotional expression, as represented by laughter and weeping, remains permanently absent, although a certain power of voluntary control may be attained.

Another interesting group of facts may be elicited by the study of facial paralysis resulting from gradual pressure, as in cases of tumour, either of the temporal bone or of the cerebello-pontine angle.

In such cases of slow compression, it is usually possible to demonstrate some loss of the isolated movements of cortical origin with preservation of automatic and associated movements.

In a patient at present under my observation with a tumour of the petrous portion of the temporal bone a facial palsy has gradually become manifest. Many of the movements of cortical origin, as for example elevation of the brow or isolated contraction of the angle of the mouth, failed to develop on voluntary effort, and yet in the natural emotional play of the facial muscles these same muscle groups were thrown into active contraction. Indeed, it would seem as though there was an emotional hyperactivity in those groups which were paralysed for cortical innervation.

It would almost appear as if the higher cortical mechanism exercised some controlling influence on the lower system, for when this is destroyed the lower system overacts. Perhaps the failure of the cortical impulses to find an outlet on account of the destruction of neo-kinetic fibres lends an added force to the contractions in the paleo-kinetic system. In any event, contractural states and overaction develop with the loss of the cortico-neural system.

I think, therefore, that a careful study of facial palsies will convince most observers that during recovery the automatic and associated movements are the first to appear, and in older cases with imperfect recovery always show a greater restoration of function; furthermore, when the facial nerve is subjected to pressure the neo-kinetic movements are those which are first lost—which would seem to favour the theory of two distinct physiological systems for the transmission of motor impulses, in the cranial as well as the spinal nerves.

Chapter III.—Anatomical Considerations.

In the foregoing chapter certain clinical evidence has been presented which would appear to indicate the existence of two distinct physiological systems for the transmission of motor impulses in peripheral nerves. This evidence would also appear to show a cardinal difference in the anatomical structure of these two systems. For the paleo-kinetic system is less vulnerable to the effects of pressure and is the first to show signs of returning function after injury to the nerve. Especial emphasis should also be laid on those remarkable cases in which the paleo-kinetic function is alone demonstrable many years after injury, when there is every reason to assume the existence of a gap or other formidable obstruction to the regenerative activities of the nerve.

All of these facts favour the idea that the paleo-kinetic function is subserved by a lower type of nerve-fibre, as it is well known that a higher differentiation of nerve structure is associated with increased vulnerability to injury and a lessened regenerative capacity.

Are there any facts in the development and finer anatomy of nerve-fibres which might bear correlation with this point of view?

The peripheral nervous system is composed of two types of nerve-fibres—medullated and non-medullated. The non-medullated is similar in structure to the medullated fibre, save for the absence of a myelin sheath. It is composed of an axis cylinder and a neurilemma, and is supposed to subserve the function of the visceral or sympathetic nervous system.

Medullated nerve-fibres vary considerably in size; some are large, others of medium calibre, and many are quite small, not greatly exceeding the diameter of the non-medullated fibre. Those medullated nerve-fibres subserving a motor function terminate in striated musculature by a special nerve-ending or a motor end-plate.

In recent years considerable attention has been given to the presence of another type of end-plate in striated muscles, which is apparently of sympathetic origin, it being the terminal of a non-medullated nerve-fibre (Boeke [2]). It would thus appear that striated muscles are innervated by two distinct systems of fibres, the one medullated and the other of non-medullated type. This theory of a dual innervation of striated muscles as enunciated by Botazzi [3] has received confirmation from other sources, chemical, histological and physiological, and is no doubt destined to play an important rôle in the elucidation of the problem of motility and the various disorders of the neuro-muscular mechanism.

It is held that the anisotropic disk system of muscles which subserves the function of the quick contraction, or the twitch, is supplied by motor cells of the spinal cord, medullated nerve-fibres and motor end-plates. The sarcoplasmic substance, on the other hand, is assumed to be innervated by the sympathetic cells of the cord, the non-medullated nerve-fibres and a special sympathetic motor end-plate.

The sarcoplasm of muscle is that component which is concerned with the slow tonic forms of muscular contractions, and is more plastic in its function.

According to this conception the slow, tonic contraction of muscular tissue is distinct physiologically from that of the quick contraction or the twitch. Langelaan [13] and Sherrington have recently made notable contributions to this subject, and Sherrington [18] has shown the relation existing between the posturing function of muscle tissue and the sarcoplasmic substance in both striated and non-striated muscles.

As the slow plastic component of voluntary muscles is similar to the function of non-striated muscle-fibres of the visceral system which are exclusively innervated by the sympathetic system, it would appear probable that the twitch component is of more recent origin, phylogenetically, and, as it were, has been superadded to the sarcoplasmic substance in the course of evolution in order to allow greater range and variety of movement. If this were true, one might anticipate a greater development of the twitch component as motility became more highly organized and differentiated, and in the isolated movements of cortical origin the sarcostyles or anisotropic disk system would play a greater rôle than in automatic and associated movements.

At the present time opinions are at variance as to the source of this sympathetic innervation of striated muscle-fibres. Certain studies

would appear to show that these fibres emerge in the anterior roots, passing in the white ramus to the sympathetic and reaching the muscles by way of the vascular system. In one group of experiments, section of the abdominal sympathetic in cats produced some diminution of muscular tonus. A similar experiment on the dog, however, was not followed by any reduction of tonus; so whatever may be the source of these non-medullated nerve-fibres and sympathetic nerve-endings in striated muscles, the interesting fact is the duality of function which appears now to be well established: the disk system, or sarcostyles, subserving the twitch or quick movement, and the sarcoplasm the more continuous contraction.

It is, I believe, not improbable that certain differences in the functions of the paleo-kinetic and neo-kinetic systems are closely related to this duality of function of the intrinsic muscle mechanism.

The higher differentiation of motility as exemplified in movements of cortical origin being largely dependent upon a greater development and finer dissociation of the anisotropic system, while in many automatic and associated activities, as of the trunk, the postural and tonic element predominates, which is the function of the sarcoplasm.

Non-medullated nerve-fibres in spinal nerves.—Of great interest in relation to the presence of non-medullated nerve-endings in skeletal muscles are the recent researches of Ransom on the histological structure of spinal nerves.

Ransom [16] by the use of a special method of silver impregnation, which he termed the silver-pyradine technique, has been able to demonstrate large numbers of non-medullated nerve-fibres in peripheral nerves. The existence of such fibres in small numbers has long been known, but that they are as numerous as medullated nerve-fibres was not recognized before the publication of Ransom's studies and his special method of staining. In some nerves they may even exceed in number those of the medullated type.

These non-medullated fibres are not gathered on the periphery of the nerve-fibre in small groups as occurs when a twig from the vascular sympathetic joins the nerve-trunk, but are uniformly diffused throughout the whole section of the nerve.

Ransom has also shown that the greater number of these non-medullated fibres pass to the skin and take their origin in the smaller type of ganglion cell in the ganglia of the posterior roots. He states, however, that a few of these fibres also pass to the muscles.

He makes the very interesting suggestion that these fibres, which

are evidently of a more primitive type than medullated nerve-fibres, may be concerned with the transmission of protopathic sensibility, which is a more primitive form of sensation and therefore would be related to a more primitive anatomical system in the nerve-trunk. The epicritic sensibility, as it represents a higher and more specialized form of sensory function, would naturally be subserved by a more specialized system of nerve-fibres.

Ransom reached the conclusion that if Head's conception of sensibility is correct, a large proportion of the afferent nerve-fibres of mammals remains in a relatively undifferentiated state and transmit a relatively primitive and diffuse form of sensation, while other afferent fibres have undergone a further differentiation, acquired a myelin sheath and are engaged in the transmission of specialized forms of sensation, including an increased power of localization.

Insulation of the axone by the myelin sheath is probably an important factor in eliminating the element of diffusion so characteristic of primitive sensation.

It would be of great interest to apply Ransom's technique to the question of the paleo-kinetic system in peripheral nerves. Here in the motor sphere is a more primitive and relatively diffused form of motility, which in its regenerative reaction to injury is not unlike that shown by protopathic sensibility. If the existence of a primeval sensory system in peripheral nerves is accepted, on theoretical grounds, there would be good reason for the assumption that a primitive motor system is also present, as both sensory and motor functions must have passed through very similar stages of specialization and phylogeny.

Ventral roots of the spinal cord.—If there exists a neo-kinetic system in peripheral nerves subserving the motor functions of the cortex, such a system would necessarily have a larger representation in the muscles of the upper and lower extremities than in those of the trunk, as the finer cortical movements are chiefly represented in the extremities. This being true one might expect to encounter certain histological differences in the fibres of the anterior roots which would correspond to the relative representation of the paleo-kinetic and neo-kinetic functions.

In the description of the ventral roots of the spinal cord as given in "Quain's Anatomy," the large and medium-sized medullated nerve-fibres are found in greatest number in the cervical and lumbo-sacral roots, the finer fibres constituting only one-sixth of the whole number in these regions.

On the other hand, the finer nerve-fibres preponderate in the thoracic and coccygeal regions in the proportion of three to one. There may, therefore, be some confirmation of my theory in these facts.

For, while the sympathetic fibres of the autonomic system undoubtedly arise at the thoracic and coccygeal levels there are the enormous muscular masses of the trunk to be innervated, and if these are supplied exclusively by medullated nerve-fibres of large or medium calibre, one would hardly expect such a great preponderance of the finer type of nerve-fibre. In this relation it is also of interest to consider the important rôle played by the muscles of the trunk in automatic and associated movements and their comparative unimportance in the finer movements of cortical origin.

Myelinization of the anterior roots.—If my theory is correct that there exists in peripheral nerves a more highly differentiated type of nerve-fibre subserving the neo-kinetic function of the cortex, one might expect such fibres to develop later than those of the paleo-kinetic system and perhaps receive their myelin sheath subsequent to birth as in the case of the pyramidal tracts.

I am aware of no systematic studies covering this field in the peripheral nervous system of man, a method which yielded such fruitful results to Fleichsig in the brain and spinal cord.

There are, however, some interesting investigations in the field of comparative neurology which would appear to show a considerable post-natal myelinization of the anterior roots.

Hatai [5] has made an elaborate study of the number of medullated nerve-fibres in the anterior roots of the white rat at different ages, and has noted a definite increase corresponding to different periods of growth. He reaches the interesting conclusion that "the total number of the medullated fibres in the ventral roots of the spinal nerves increases as the animal becomes older. The rate of increase of these fibres is not the same for the different ages. It is most rapid between the weights of 10·3 and 25·4 grammes (ten to thirty days), after which it becomes slower. The total number at maturity is about 2·7 times that found in the 10·3-gramme rat."

He also states that "at all ages the ventral root near the cord contains more medullated fibres than appear more distally, the second section being taken near the ganglion of the corresponding dorsal root; in other words, the total number of the medullated fibres in the central root decreases from the spinal cord towards the periphery."

It is possible that these findings may bear some correlation with a

higher specialization of motor function in peripheral nerves, as the age of myelinization is of paramount importance in indicating the phylogenetic relationship of the various neuronal systems. This is manifested in the corpus striatum, for example, by the early myelinization of the ansa system and in the cerebral cortex by the late development of the pyramidal tracts, and if specialization of function leaves its imprint in this manner on the central nervous system one might anticipate similar results in the peripheral pathways.

Boughton [4] also investigated this question in the oculo-motor nerves of the white rat and has reached somewhat similar conclusions. He states that, "in white rats having body weights of 11 grammes and 414 grammes, there is a nearly regular increase in the number of medullated fibres in the oculo-motor nerves, this increase amounting to 75 per cent."

In this brief sketch of certain histological evidence I would simply indicate in a very general way the possibility of an anatomical basis for these two physiological systems.

It is my belief that they are anatomically distinct, and the proof of my clinical interpretation must await further study along these and other lines, for in the elucidation of finer anatomical problems a knowledge of function must often precede its structural demonstration.

Chapter IV.—The Relation of the Neo-kinetic and Paleo-kinetic Systems to the Classical Types of Central Hypertonus.—Spasticity and Rigidity.

The conception that skeletal muscles are innervated by two physiologically distinct motor systems, subserving paleo-kinetic and neo-kinetic functions of motility, is not without interest in its relation to questions of hypertonus.

Two great types of hypertonicity are recognized; a spastic state which is referable to the cortico-spinal system, and the rigidity of paralysis agitans which I would refer to the strio-spinal pathways [9]. Is there any relationship existing between these central types of muscular rigidity and the paleo-kinetic and neo-kinetic functions of motility?

It is an established fact of physiology that separation of the motor cortex from the lower spinal centres removes a certain restraining influence termed inhibition, which is characterized by a peculiar spas-

ticity of the musculature. If, as I assume, the corpus striatum is the higher regulating and correlating centre of the extrapyramidal motor systems, it should also exercise an inhibitory influence on the lower motor neurones with corresponding evidences of hypertonicity if the restraining influence were removed. Thus both correlating centres, cortical and striatal, would exercise inhibitory control over their respective spinal centres, which, when abolished, would be followed by the phenomena of hypertonus. In the cortico-spinal system this would take the form of spasticity, and in the strio-spinal system that of rigidity—both spasticity and rigidity constituting a hypertonic condition of the musculature, presenting, however, certain distinguishing features.

There are many differences between these two forms of hypertonus which would lend weight to the theory of a paleo-kinetic and neo-kinetic innervation of striated muscles.

These differences in the character of the hypertonicity, I believe, are dependent upon the relative representation of the two intrinsic contractile systems of skeletal muscles—the anisotropic disk system and the sarcoplasm: that of the disk system (sarcostyles) predominating in neo-kinetic motility, and the sarcoplasmic substance playing an important rôle in paleo-kinetic types of motility.

In lower types of movements such as are represented in paleo-kinetic motility there is a large postural or tonic component greater than in isolated synergic movements of cortical origin where a finer individualization of movement is required, with a consequently greater development of the disk function.

In all forms of muscular activity both the tonic and contractile components are represented, but the higher differentiation of motor functions in cortical movement is produced by a predominance of the contractile or quick movement which is dependent upon the sarcostyles of the disk system.

In the higher development of motility, as it is found in the motor cortex, there is a greater utilization of the contractile element as contrasted with the tonic or plastic element in order to attain a more definite and discriminative control of movement.

It would appear as if the higher differentiation of movement is in the direction of dissociation as compared with the more massive associated movements of involuntary character which are largely engaged in walking, running, posture, grasping, &c. In all such motor acts there is an enormous preponderance of massive contractions of a large number

of muscles in contrast to the more diversified, disseminated acts of cortical origin; the paleo-kinetic motility is preponderantly sarcoplasmatic, while the neo-kinetic motility has more the contractile character. For example, an extension of the index finger is produced by an isolated contraction of the agonist with simultaneous relaxation of its antagonist. A grasping movement of striatal origin, on the other hand, is characterized by a diffuse massive contraction of practically all the muscles of the hand, forearm and arm, a form of movement which differs fundamentally from a dissociated movement of cortical origin.

Deformity.—One of the most striking results of a lesion of the pyramidal tract is the deformity and attitude of the paralysed members.

In unilateral lesions the attitude corresponds to what has been termed the Wernicke-Mann type of hemiplegia, viz., adduction of the arm, flexion of the elbow, pronation of the hand and flexion of the thumb and fingers. The lower extremity is fixed in extension with overaction of the triceps suræ, producing the pointed toe deformity. The face is paralysed save for those muscles which act symmetrically, as the frontalis and orbicularis palpebrarum, while the emotional innervation is preserved.

A careful study of this form of paralysis with its associated spasticity will, I believe, demonstrate the loss of the neo-kinetic function of motility, the type of the spastic contraction corresponding to the release of the peripheral neo-kinetic systems, or that system of fibres which subserve the function of isolated cortical movements.

A study of a large series of old infantile hemiplegias at the Craig Colony for Epileptics, in which the lesions were essentially cortical, has convinced me of the preservation of the automatic and associated movements on the paralysed side. The paralysis is one purely of neo-kinetic motility. It is for this reason, I believe, that the extremities and chiefly their distal portions, and more especially the hand, show the greatest degree of paralysis and spasticity, as this portion of the musculature presents the highest degree of specialization in the realm of cortical movements. It also explains the relative freedom of the trunk muscles and the root segments of the extremities which are chiefly concerned with the automatic and associated movements of posture, gait, and station.

Contrast, for example, the disturbances of gait, the difficulty in rising from the recumbent or sitting posture, and the paralysis of expression in paralysis agitans and the preponderant involvement of the extremities, and more especially their distal portions in the spastic palsies of cortical

origin. While both types of paralysis involve to some extent the whole skeletal musculature, that of the trunk and root segments predominates in the strio-spinal type and the distal portion of the extremities in the cortico-spinal type, due, as I believe, to the character and distribution of the peripheral paleo-kinetic and neo-kinetic systems.

Rigidity.—The rigidity of paralysis agitans differs in its quality and distribution from the spastic state, although presenting the common characteristic of a central hypertonicity.

The increase of tonus is more uniform and of a more waxy character. It is more plastic, and lacks the elastic quality of spasticity—the so-called clasp-knife rigidity—and there are none of the associated symptoms of increased contractility such as clonus and exaggeration of the tendon reflexes.

The deformity and attitude are also quite different: as is evidenced by the slight flexion of the arms and legs, the bent head and body, the mask-like expression of the face, and the interosseal position of the hands. The alteration in attitude and the rigidity of the trunk are very striking features when contrasted with the characteristic deformity of the extremities which characterizes the spastic state.

These peculiarities of the rigidity in paralysis agitans I would refer to the special function of the paleo-kinetic system with its control over automatic and associated movements which are so closely related to gross movements of the extremities and trunk in their relations to posture and progression. Therefore, when the paleo-kinetic system is released from the inhibitory control of the corpus striatum only those peripheral neurones which subserve the paleo-kinetic function of motility are affected with the characteristic distribution of the rigidity and evidence of a relative preponderance of the sarcoplasmic innervation,

The paralysis of this group of cases is one of automatic and associated activities of muscles; and the isolated movements of cortical origin are well preserved, being merely masked by the rigidity of the musculature.

For in this dual innervation of the striated muscles (paleo-kinetic and neo-kinetic) a paralysis of either system, with its resulting hypertonicity, sadly interferes with the functions of the other motor system, which may be quite intact.

In advanced cases in which the hypertonicity has reached a high degree, with fixation of the joints and tendinous structures, the remaining system may be practically useless although retaining its functional power.

In this conception of a dual innervation, I would maintain that each skeletal muscle may be independently contracted through one or the other system, and that the functional loss of either by causing hypertonicity exerts a considerable interference with the function of the remaining system.

Therefore, in the classical types of central hypertonicity, I believe there is strong corroborative evidence of the existence of two separate physiological systems for the transmission of motor impulses in peripheral nerves.

There is a neo-kinetic system for the transmission of isolated movements of cortical origin which has reached its greatest development in the extremities, and especially the human hand. For this reason the spastic contractures are especially pronounced in this portion of the skeletal musculature. The neural control of the anisotropic disk system has reached a higher degree of development in the neo-kinetic system which is evidenced by the clonus, the more elastic quality of the rigidity and the exaggerated tendon reflexes—all indicating a greater development of the contractile element of motility, as contrasted with its more plastic function (sarcoplasmic substance).

The paleo-kinetic system, on the other hand, subserves a lower type of motility which is characterized by automatic and associated movements and is presided over by the corpus striatum. This form of innervation is preponderantly sarcoplasmic which harmonizes with the nature and quality of automatic and associated acts, hence the waxy rigidity of the hypertonus, the characteristic deformity, the absence of clonus and tendon hyperexcitability.

Reflex activities in central types of palsy.—If there exists in the central and peripheral nervous system two great physiological systems of fibres for the transmission of motor impulses of cortical and striatal origin one would expect to encounter certain reflex activities referable to one or the other of these two systems.

The specialization and differentiation of the pathways would be accompanied by a corresponding development and specialization of certain spinal reflex systems—the differentiation of a strio-spinal and cortico-spinal system developing simultaneously with a corresponding spino-neural mechanism. For it would be difficult to conceive of a spinal mechanism which would functionate effectively in the operations of motility without certain of its systems undergoing further development to meet the requirements of the higher central functions. In this way reflex spinal activities would develop which

would be related to the striatal and cortical functions and would therefore represent a higher order of spinal mechanism than that of the primitive segmental function of the cord.

What is the state of the reflexes in paralysis agitans and do they shed any light on the existence of a paleo-kinetic system?

First, it is worthy of emphasis that the skin reflexes, e.g., the plantar reflex, the abdominal and cremasteric reflexes, preserve their integrity unchanged until a late period of the disease, when they may suffer some diminution from the purely mechanical conditions of rigid musculature.

This preservation of the skin reflexes I consider of great importance as indicating their probable relationship to the neo-kinetic system. It would appear that the paleo-kinetic system is not concerned with transmission of the impulses underlying the cutaneous reflexes. This form of reflex activity is apparently of a higher type, the afferents being probably related to Head's epicritic system, and the efferents to the central (pyramidal tracts) and peripheral neo-kinetic systems.

The tendon reflexes are also preserved in paralysis agitans and, as a rule, show no special abnormalities. In those types of the disease in which the tremor manifestations predominate, and there is but little rigidity, they are quite frequently exaggerated, but never to the same degree as in purely spastic states.

There are never the associated clonic manifestations, e.g., ankle clonus, patellar and wrist clonus which characterize the spastic type of hypertonicity, and yet the resemblance of the spontaneous rhythmical tremor to the spastic clonus may be mentioned, as I would refer both to the activity of the disk system in contradistinction to the rigidity which is referable to the more plastic and tonic functions of the sarcoplasm.

As rigidity increases with the progress of the disease the tendon reflexes undergo some diminution, due apparently to the increased tonicity of the sarcoplasm. They can, however, usually be elicited, even in a late stage of the affection.

The reflexes in spastic paralysis—After lesions of the cortico-spinal systems (pyramidal tracts) the state of the reflexes is quite different.

The abdominal and cremasteric reflexes are abolished, even when this system is involved in the cerebral cortex itself. This would appear to show that these reflexes have long reflex arcs which pass to the cerebral cortex by way of a cortical afferent system, the efferent impulses then descending the motor tracts to the periphery.

According to my conception these impulses would pass to the cortex by way of Head's epicritic system, and then descend to the pyramidal tracts and the neo-kinetic system in peripheral nerves.

The same is true of the normal plantar reflex. In pyramidal tract disease this is replaced by the Babinski responses which I believe is of striatal or strio-spinal origin. This is an older type of plantar reflex which is present in the newborn, and later is replaced or inhibited by the further development of cortical control.

Other reflexes which are elicitable in pyramidal tract disease, such as the combined flexion of the hip, knee and ankle (Strumpel's tibial phenomenon) I believe are also of striatal origin and reproduce the stepping movement which is one of the automatic associated functions of the corpus striatum—the strio-spinal mechanism.

Very striking is the great exaggeration of the tendon and periosteal reflexes in spastic states and the various clonic manifestations, viz., ankle clonus, patellar and wrist clonus.

These phenomena I would ascribe to the greater activity of the sarcostyles in the isolated movements of cortical origin, so that when released from inhibition there results a greater reflex twitch reaction than when the extrapyramidal system suffers a similar release. It is possible also that the sarcoplasm plays a more subordinate rôle in cortical activities which would allow a greater freedom of the twitch contraction.

It is also not without significance that the exaggeration of reflexes is greatest in the extremities and especially the distal portions, which would correspond to the highest development of cortical movement.

In pyramidal tract disease it is interesting to compare the exquisite exaggeration of the tendon and periosteal reflexes of the hand which represent par excellence the highest cortical function of motility with those elicited from the trunk or cephalic extremities; and also the distribution of the hypertonicity in spastic states to the distribution of the various tendon and periosteal reflexes and their very evident territorial relationship to the muscles subserving the highest functions of cortical motility.

It would therefore appear that in the various reflex activities which accompany palsies of strio-spinal and cortico-spinal origin, there is perhaps also some confirmation of my hypothesis of a paleo-kinetic and neo-kinetic system for the transmission of motor impulses in peripheral nerves.

Chapter V.—Concluding Remarks.

In the evolution of the nervous system progress in the domain of motility is represented by the development of certain fundamental types of movement long recognized by physiologists.

This evolution in the sphere of motion shows very clearly the struggle of the organism to acquire a greater independence of action in relation to the outer world. Simple reflex motility was followed by the more elaborate type of automatic and associated movement and this in turn was succeeded by the highly specialized movements of cortical origin.

Primitive reflex motility is purely spinal and is referable to the various units of the segmental nervous system.

Movements of the isolated synergic type are cortical in origin and are subserved by a cortico-spinal system, the pyramidal tracts.

I have already presented evidence for the assumption that automatic and associated movements are subserved by a strio-spinal system, the controlling mechanism of which is the corpus striatum and the conductive pathways, the extrapyramidal motor tracts.

Thus there are spinal, strio-spinal and cortico-spinal types of motility, all associated and working together harmoniously and representing different stages in the development of the nervous system.

According to the hypothesis formulated in the present study these subdivisions are not confined to the central nervous system but are continued as such in peripheral nerves. The peripheral motor neurones would therefore include two separate and distinct physiological systems related respectively to the strio-spinal and the cortico-spinal systems.

The older of these, the paleo-kinetic system, is engaged in the transmission of the motor impulses of automatic and associated movements, while the more recent neo-kinetic system conveys the motor impulses of cortical origin.

In other words, with the specialization of the central pathways there has been a corresponding specialization and differentiation in peripheral nerves, with the development of separate systems of fibres for striatal and cortical functions. I would therefore recognize a continuous cortico-spino-neural system subserving a neo-kinetic function and a strio-spino-neural system subserving the function of paleo-kinetic motility.

For reasons which have already been expressed I regard it as highly probable that these two systems present anatomical differences which

explain their respective reactions to injury—the nerve-fibres of the neo-kinetic system presenting a higher degree of specialization than those of the paleo-kinetic system, thus causing a greater vulnerability and lessened regenerative eapacity.

It is, I believe, not without significance that Henry Head has reached somewhat similar conclusions after an exhaustive study of the afferent system, for specialization and differentiation in both the motor and sensory spheres would naturally follow similar pathways in the upward struggle of the organism.

It is my belief that these two motor systems are associated with the development of corresponding reflex activities, so that strio-spinal and cortico-spinal types of reflexes may be recognized. The differentiation of each system is therefore associated with a corresponding differentiation in the spinal mechanism, which may express itself in the form of special forms of spinal reflexes.

It would also appear that certain differences in the two classical types of central hypertonus, spasticity and rigidity—e.g., the distribution and nature of the palsy, the associated deformity, the character of the hypertonicity and the alteration in reflex activity—may be explained on the basis of their relationships to the neo-kinetic and paleo-kinetic systems.

Of special interest is the apparent preponderance of the disk system or sarcostyles in neo-kinetic motility as contrasted with that of the sarcoplasmic function which predominates in paleo-kinetic motility. This suggests that the more highly specialized forms of movement may be associated with an increased functional activity of the disk system.

Much that is now obscure in the occurrence of so-called associated movements following various types of central lesions will, I believe, find their explanation in the conception of a strio-spinal and cortico-spinal system.

Certain associated movements represent simply the return of the original bilaterality of cortical movements which have undergone suppression in the infantile period, while others are frankly related to the striatal mechanism.

The close relationships of the cerebellar function to motility is recognized by all observers. According to the best authorities the cerebellum is an organ which controls muscle tonus and the synergies of movement and is closely related to posture and equilibrium. In recent years, considerable attention has been given to the question of cerebellar localization.

It will, I believe, be fruitful to consider this organ in its possible relation to a paleo-kinetic and neo-kinetic function.

In all forms of motility two components are readily recognized—a kinetic and a static or postural.

The kinetic component is the movement proper, while the static component is that plastic quality of muscle which maintains posture. Posture is present both during rest and during movement, for in every active movement there is a certain stability or postural element which is an essential part of the motion complex.

Here, again, I believe two great functional divisions may be recognized subserving a strio-spinal and a cortico-spinal postural function—the essential organ for the control of which would appear to be the cerebellum.

According to this conception, there is a paleo-cerebellum which controls the postural or static function of automatic and associated movements and a neo-cerebellum for the postural control of isolated synergic movements of cortical origin.

Comparative neurologists have long recognized the existence of a paleo-cerebellum and a neo-cerebellum, the cerebellar hemisphere increasing in size and importance with the development of the cerebral cortex.

The intimate relation of the cerebellar hemispheres of the cerebrum is also shown by the existence of tracts passing between the cerebral cortex and the pontine nuclei which afford direct connexions with the contralateral cerebellar hemisphere.

I would therefore advance the theory that the postural or static component of movement is controlled by the cerebellum and that here also a paleo-kinetic and neo-kinetic function may be recognized, the one standing in relation to the strio-spinal system and the other to the cortico-spinal system.

The paleo-kinetic and the neo-kinetic types of motility would therefore be represented by distinct physiological systems in both the central and peripheral nervous systems, inclusive of the cerebellum.

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OBSERVATIONS ON THE SENSUAL RÔLE OF THE PROPRIOCEPTIVE NERVE-SUPPLY OF THE EXTRINSIC OCULAR MUSCLES.

BY C. S. SHERRINGTON.

THE rich supply of afferent nerve-fibres existent in the muscles which move the eyeball invites inquiry as to what may be the contribution which these nerves make to visual reactions. Their reflex function should, like that of other proprioceptives, relate to the adjustment and maintenance of postures. Ocular posturing, such as the adjustment and maintenance of the gaze, is delicate and almost continual throughout the waking day. And the afferent nerves from muscles, as is known of them from other muscular fields, yield besides their purely reflex taxis of local posture and movement, sensory impressions which are the basis of perceptions of postures and movements, in short subserve muscular sense. Muscular sense being, along with vision, touch, and the "labyrinthine" sense, a chief source whence the mind manufactures sensual "space," the above is tantamount to saying that the proprioceptive nerves of the eyeball muscles may be expected to contribute to space as perceived with the eye. In the literatures of muscular sense and of visual perception one does not however find, at least so far as my acquaintance with those literatures reaches, much advertence to a spatial rôle for the eye-muscle afferents, and if adverted to, such a rôle for them is often not acceded to. For this attitude of negation towards them, two circumstances are probably largely responsible. The spatial endowment of the retinal sense itself is of such pre-eminent and exquisite degree that it has seemed, especially under more recent investigations, a sufficient source in itself for almost every spatial attribute of vision. The likelihood therefore that adjuvant factors of non-retinal origin make any important contribution to visual space has seemed small. Again, the demonstrated existence of a wealth of afferent nerve-fibres in the eye-muscles is a discovery of comparatively recent date. At the time of the studies of visual space-perception by Wells, Panum, Lotze, Aubert, Hering, and others, the possession of muscular sense by the eye muscles, although on general grounds probable, had no proven neurological basis.

Yet, that a sense-datum derived from the external muscles of the eyeball does furnish factors of importance in visual space, even in uniretinal vision, is, I think, demonstrable by extremely simple experiments. Recourse to certain old and often repeated observations seems sufficient to show this, if the findings be reconsidered from the proprioceptive standpoint.

An observation of such a kind is the following: With the head erect let three spots A, B, C, be looked at directly in front, for instance, on a bare wall across the room. Let us suppose one eye only to be used, the other closed. Let the three spots be equally spaced and in one vertical; and suppose the middle one B the point of visual fixation, and at the level of the eye so that the eyeball is in the so-called "primary" position. Suppose A to lie above B and C below B. The spots are perceived as forming one vertical. How is their verticality recognized? An answer often accepted is as follows: The spots stimulate three retinal points α, β, γ, the mental reactions attaching to which give sensual "verticality" as an attribute inherent in the perception of those points taken as a group. Let us test this statement. Without moving the head, let the eye be directed toward three similar spots A′, B′, C′, on some other part of the wall, say higher and to the right, and lying in one vertical, and let the middle one B′ be fixated.

For strict demonstration the plane surface toward which the gaze is directed should, as in the strict demonstration of Listing's law, be perpendicular to the line of vision, which it will not be if the wall is used for the secondary eye-posture as well as for the first. The well-known slight "perspective" deviation then complicates the Listing so-called "false" torsion. A flat screen set perpendicular to the direction of the visual line in the secondary posture chosen for the eye obviates this.

Then these three spots are perceived likewise as situate in one vertical. But Listing's law of the postures of the eyeball tell us, and its demonstration proves to us, that in this second case, although the spot B′ stimulates the same retinal point β as did B, the spot A′ does not stimulate the retinal point α as did A, but a retinal point α' lying to right of α, and the spot C does not stimulate retinal point γ, but a point γ' lying to left of γ.

We have therefore on the above offered explanation a dilemma. The explanation says that an inherent quality attaching to the three retinal points α, β, γ, gives them as a group verticality in visual space. It says the same of three retinal points α', β, γ' which lie in a retinal line inclined to and crossing at β the line formed by α, β, γ.

If it be doubted that the line of retinal points stimulated by spots A′, B′, C′ is really oblique to and crossing the line of retinal points stimulated by A, B, C, we have only to obtain the after-images of A′, B′, C′, and turn the fixation of the eye back to B. The projected after-image of A′ then appears to the left of spot A, and the after-image of C′ to the right of C, and the line connecting the after-images of A′ and C′ runs obliquely through B and appears no longer vertical but at an angle to the vertical. Though seen as vertical when the eyeball was in the secondary position, namely, gazing upwards and to the right, it is now, with the eyeball in the primary position, seen as if it had undergone an anti-clockwise rotation round its middle point. Conversely if the after-images obtained in the primary ocular position from spots A, B, C are projected when spot B′ is fixated, that is with the eyeball in the given secondary position, the line they form no longer appears vertical, but is seen as inclined to and crossing the vertical line formed by A′, B′, C′, as if it had suffered a clockwise rotation round its middle point.

Thus it is clear that verticality is no unalterable inherent sense-datum attaching to the retinal point-group α, β, γ, as such; for, though in one position of the eyeball that group says inalienably "vertical," in another position of the eyeball it says "inclined to the vertical," namely, in this particular case, upwards and to the right. And the like is conversely true of the other line of retinal points α', β, γ'. Indeed, as the ordinary after-image method for demonstration of Listing's law shows, there is no oblique posture of the eyeball in which the after-images belonging to A, B, C, do appear truly vertical. When the gaze is upward to the left the row they form leans up to the left, when the gaze is downward to the right the row leans downward to the right, and when the gaze is down to the left the row leans downward to the left. The inclinations are in fact both in sense and degree those of the well-known findings that demonstrate Listing's law.

The spatial reference, therefore, of a rectilinear row of retinal points, e.g., α, β, γ, says "vertical" *conditionally*. What condition decides it to affirm verticality in some circumstances, non-verticality in others? In other words, on what factors is based its decision discriminating between vertical and non-vertical? For simplicity of statement the discussion may be restricted to the one experiment where, firstly, the vertical row of spots, A, B, C, is fixated, and, secondly, the gaze is then, without other movement than that of the eyeball, turned upward to the right for observing the projected after-images.

The first stage of this experiment may be called obs. 1, the second obs. 2. What is the difference of sensual conditions obtaining between obs. 1 and obs. 2 respectively?

Evidently the only essential difference between them is that the posture of the eyeball has changed. Unless we suppose that the eyeball-muscles, unlike all other striped muscles, are unprovided with muscular sense, the new posture which they have assumed, and given to the eyeball, must be registered and perceptible. And the presumption is high that these muscles are liberally endowed with muscular sense, for they are known to be supplied copiously with proprioceptive nerves—the very system of nerves which in other muscles is the basis of muscular sense. If in an entirely dark room we direct the eyeballs in this direction or in that, we, although without retinal guidance, are still aware of the directions given to the eyeball. And this is so even when the whole front of the eyeball and the inner surface of the lids have been rendered insentient by cocaine. The direction of the eyeball is then judged almost as accurately as with use of the retina in the undarkened room. Such appreciation of the posture of the eyeball must be attributed to muscular sense. The experiment under discussion may therefore be stated thus: In obs. 1 the sensation from the retinal point-group α, β, γ, is accompanied by a muscular-sense impression p from the extrinsic ocular muscles, an impression attributive to their postural state at that time, namely, to the so-called primary position of the eye. In obs. 2 the similarly evoked retinal sensation from the same retinal point group is accompanied by a muscular-sense impression from the eye-muscles which is not p but p', attributive to a different postural state obtaining in them, namely, that of the given so-called secondary position assumed by the eyeball in obs. 2. The sensual complex is different, and the resulting perception differs accordingly. Evidently what we might suppose at first acceptance to be a purely visual perception is, in fact, the result of a fusion of retinal sensation with eye-muscle posture-sensation.

Granting this, can there be distinguished in these perceptions, which we may still call visual, the spatial elements which are purely retinal from those to which muscular sense is adjuvant? Let us leave aside, as not germane to the present question, perspective and third-dimensional features, as far as any such attach to these observations, arranged as they are to be as stripped of them as practicable. The spatial features then attaching to the perceptions are briefly as follows: In obs. 1 (1) three spots of a certain size and shape; (2) situate equi-

distant; (3) on one rectilinear axis; (4) which axis is "vertical," and (5) directly in front of the observer. If any of these features persist from obs. 1, unaltered into obs. 2, we may infer securely that muscular sense of the eyeball muscles is not involved in them. Of the above five features (1) (2) and (3) do continue unaltered in obs. 2; they are, therefore, space-attributes of purely retinal origin. But (4) and (5) have undergone modification in the perception belonging to obs. 2, as compared with that of obs. 1. The row of spots, as seen in obs. 2, is no longer vertical, as it was in obs. 1, but is inclined to the vertical. And in obs. 2 the row is seen not directly in front of the observer, as in obs. 1, but is seen above and to the right. Therefore (4) and (5) are based on fusions of retinal sense with ocular-muscle sense. They may be *called* visual because natively apprehended to be such, but their source is not purely retinal.

A tactual analogue may serve in illustration. Let three points, say the prong-tips of a trifid fork, be set against the skin, e.g., of a finger, by some other person and with one's eyes closed. One can perceive tactually not only that the points are three, and that they lie equidistant in one straight line, but, with approximate correctness, the orientation of that line to the vertical—also, of course, the whereabouts in the field of reach of the hand at which the touch is met. In this case the contribution made to the spatial perception by the muscular sense is well known and no longer debated. The recognition of the whereabouts in the arm's field of reach is based on the muscular sense of the arm, which tells us the arm's posture, e.g., whether outstretched or not, whether outstretched to right or left when the touch is met with, &c. So also with the recognition of the orientation to the vertical of the line of the three touches. Thus, if the line of the prong-tips be set parallel with the finger's long axis, and the finger be vertical when the touches are received, we perceive the line of touches as "vertical." The postural muscle-sense of the arm, including the finger, is here, of course, the factor which gives the touch-row verticality. If the finger be horizontal when the same three skin-points are touched, the touches say "horizontal." Although the touch-loci have not been changed, the concomitant muscle-sense datum—the finger posture—has changed, and the touches now report "horizontally," e.g., of the line of prong-tips, where formerly they reported "vertical."

The analogy between the tactual and the visual results is obvious. Further, the tactual example makes perhaps more evident another sensual factor involved similarly both in its own and in the visual

problem, a factor whose consideration was postponed for the time being in the above statement of the two cases. The evaluation of the posture of the arm in relation to surrounding objects is based upon two sets of proprioceptive data. The impulses from the proprioceptive nerves of the limb itself originate the sense-data concerning the posturing of the limb itself, the local posture as it has been termed. But at the same time the proprioceptive nerves of the rest of the body, and especially those of the gravitational labyrinth, are registering the attitude of the whole body and its orientation to the vertical. Perception of the local posture of the limb, e.g., whether its pose is flexion or extension, gives no definite knowledge of its orientation unless there is concurrent perception of the attitude and orientation to the vertical of the rest of the body of which that limb is an appendage. If one leans the trunk to the right, extension of the right arm thrusts the hand toward the ground; if one leans the body to the left, extension of the arm thrusts the hand away from the ground. To orientate, therefore, by a touch with the hand the position in which an object lies, the local muscular sense of the limb is not enough; there must be combined with it the proprioceptive perception of the posture and gravitational orientation of the rest of the body. The previously made statement of the perceiving of the whereabouts of the fork-prongs relatively to oneself has to be amplified as to its factors. In addition to T, the three touches, with purely tactual local signature, and to the sense-datum given by the arms, including the finger's, own posture, there is a third, P, the sense datum of the attitude and gravitational orientation of the rest of the body. So similarly in perceiving whether the row of touches is in a vertical or a horizontal line. The factor p, the local limb posture, says nothing decisive about verticality unless combined with factor P. But in the instance cited above factor P remains unchanged throughout the observation, as also do the three skin-points touched. The only change is p, the posture of the limb, i.e., the finger; the line of the touches is perceived vertical when the finger is vertical, horizontal when the finger is horizontal.

Returning to the visual observations, a like explanation holds. The sense-datum derived from eyeball muscles gives the "local" posture of the eyeball, i.e., the attitude of the eyeball in relation to the head. But in order to evaluate the direction in which the seen object appears the sense-datum p of the "local" posture of the eyeball in the head is not enough. With it must be combined the sense-datum P of the posture and gravitational orientation of the head itself. The sense-

datum p is indecisive as to the "direction" from the seeing self of the thing seen, and about the relation of a seen line to verticality, unless it be linked to P. But throughout the instance of visual observation which was chosen for discussion P remained unchanged. The head was fixed and the direction of uniocular gaze was shifted only by shifting in the orbit the local posture of the globus. Also, as said above, the three retinal spots were throughout the observation the same spots. The difference of spatial attributes between the perceptions belonging to the two stages of the observation are therefore due to change in the factor p, i.e., the sense-datum from the ocular muscles, the only factor which does change. The change observed in spatial attribute of the perception was twofold. In the first part of the observation the three spots appear directly in front of oneself, in the second part they appear to the right and above. In the first part they report the line they lie in to be vertical. In the second part they report it inclined, i.e., obliquely upwards to the right. Muscular sense attributive to the extrinsic ocular muscles is therefore a source of certain of the space-attributes of visual perception. It contributes to perceptions of the direction of the regarded object as projected by the observer. It is also one of the factors deciding the apparent verticality of a visual line or of that line's degree of obliquity to the vertical.

Lotze, when introducing the now generally adopted term "local sign," wrote luminously, "by 'local sign' I mean that the position of the stimulated sensual point acts on the mind." The term in its practical application to-day has come, however, to be employed for something more restricted than spatial reference as a pure generality. It is employed for spatial reference to a locus in that combined space-system composed from the so-called spatial senses, e.g., vision, touch, muscular and labyrinthine senses. Indeed, it seems inappropriate to use it for spatial attributes not referred to that common system of so-to-say ordinary workaday sensual space. Henry Watt's theory of a spatial reference constituting the basis of tonal pitch conceives a space reference not orientated in the common workaday space-system of the other senses. In Watt's view tonal pitch is an ordinal arrangement of space-signs giving merely degrees of distance between sensations of auditory modality and so generating impressions of movement but wholly devoid of orientation of position in reference to space perceived by us through other senses. To call the spatial reference in such a case "local sign" seems inadvantageous.

But the space-reference of vision has always orientation in common

sensual space. If the position of the stimulated sensual point acts, as Lotze said, on the mind, e.g., in the retina gives visual local sign, it may be expected that where muscular action determines, as with the retina, the position of the stimulated point, a muscular-sense factor will intrude itself into and be, so to say, contained in the "local sign."

Two degrees of visual localization have been long discriminated. The one, localization relative to the fixation point; the other, localization of the fixation point in reference to the observer. The former is often termed "relative" localization, the latter "absolute" localization. The simple observations forming the theme of this paper argue that the principle underlying the difference between these two kinds of local sign in vision is that muscular sense is a factor in the one and not in the other. That muscular sense is not a factor in relative local sign is tantamount to a recognition that where the space-relation between one sensory point and another cannot be altered by a muscular act, that muscular act contributes nothing sensorial to the perception of the space-relation between the points. The extrinsic muscles of an eyeball move and posture that eyeball's retina as a whole and cannot alter the mutual space-relations between points composing it. In the observations adduced in this paper the sensual line of points retains its intrinsic pattern unmodified by the posturing of the eyeball. The relative local signature of those points is unaltered by altering the muscular sense concomitant in the perceptions. Such local signature may be termed "pure retinal" local signature, because able to be regarded as pertaining to the retina itself purely.

Lotze, it will be remembered, entered upon, indeed raised, the interesting question as to how the retina has come to be endowed with its "relative," or as termed above, "pure" local signature. That question is no part of our problem. But the view he advanced does possibly affect the suitability of the term "pure retinal" signature as equivalent to "relative" local signature. It does so because Lotze attributed the genesis of relative local sign to central sensations of eye-movement and sensations of effort accompanying or forerunning those. He argued that in the retina the distance and direction from the fovea of a peripheral point has become established as a sense-attribute to that point owing to accumulated experience of the degree and kind of central motor discharge necessary for moving the fovea so as to receive the objective image previously received by the peripheral point. He supposed in short that the "relative local sign" attaching to a retinal point has its origin in a long history of experience of muscular

sense—not muscular sense as now usually understood with the commotation of peripheral proprioceptive source, but muscular sense in that older and now less prevalent acceptation, implying a "central sensation" gauging the degree and direction of motor discharge. Lotze's view is adverted to here merely to make clear that its appeal to a kind of muscular sense in its attempt to explain the genetic history of "relative" local sign is not touched by the argument we are now following. Hering explicitly denied to muscular sense any share either in relative or in absolute local sign. As regards relative local sign, apart from its possible past genetic history, on which this paper has nothing to submit, the argument of the present paper is in agreement with Hering.

But with regard to absolute local signature the case is different. The principle emerged above that where a muscular act cannot alter the space-relation between two receptive sensory points, its proprioceptive sensation does not affect or enter into the perception of that space-relation. Conversely, where a muscular act does alter the space-relation between two such points its sensation does enter in the perception of that space-relation.

There is a spatial point in the head which Hering termed the "basal point of vision." "The head, or more exactly the place where, with reference to the object viewed, we imagine our head to be, forms the centre of visual perception." The position of this point may be defined as corresponding with the centre of rotation of Hering's cyclopean eye, or briefly paraphrasing, the cyclopean point of outlook. Though a subjective point, it corresponds with a material point; this latter, as Hering showed, lies in the mid-sagittal plane of the head. And in that plane its position is where that plane is intersected by a line joining the centres of rotation of the two eyeballs right and left. The movements and postures executed by the extrinsic ocular muscles affect the spatial relation between their retina and this material point. Therefore, into the visual space-signature which refers to spatial relation between the perceptual object and the point of visual outlook, there will enter the muscular sense attribute of the movements and postures executed by the extrinsic ocular muscles. Hence, in the observations cited above, a change confined to alteration of the posture of the eyeball brings a change in the "absolute" local signature, a change in the spatial reference of the retinal point. The sensation pertaining to the stimulated retinal point is projected to a locus in sensual space surrounding the subjective point of outlook, and that locus shifts with shift in the eye-

ball's posture. The absolute local signature has therefore in it a muscular sense factor derived from the extrinsic ocular muscles.

There remains obviously a further element in visual space-assignment. Lotze says, were vision our sole sense our visual field would be an expanse without upper or lower or right or left, and for the same reason that no one in thinking of the universe as a whole regards it as being erect or vertical or horizontal, inclined, &c. Yet, in visual perception, among the seemingly elemental features of it are verticality, horizontality, &c. We have to consider on what this orientated nature of visual space is based. In the simple observations, the subject of this paper, when the retina has passed from the primary visual posture to the oblique secondary, and by so doing has arrived at a posture exhibiting the so-called "false-torsion" of the authors, objective verticality is still perceived, although through partly a new line of retinal points. The only other change in the conditions of the observations is the altered muscular state and altered muscular sensation attaching to maintenance of the eyeball in its new posture, namely, the oblique secondary posture.

That is a proprioceptive factor. Now, obvious considerations urge that the main agency by which the environment impresses upon sense its orientation translated by the mind as right-side-upness or deviations therefrom, is gravitation, i.e., the direction of the line of gravity. This seems indeed the only direct environmental influence by which that orientation becomes an immediate sensual datum. It is the only one which in so far as concerns that orientation causes reflexes directly and *per se*. In some fields of musculature gravity undoubtedly affects physically the muscular reactions in considerable measure, although whether reflexes or sensations are thereby excited is as yet insufficiently known. But the muscles of the eyeball constitute a field of proprioception which gravity can hardly affect more than so slightly as to let one suppose its influence there must be of negligible degree. There is, however, an organ, the otic labyrinth, definitely reacting to gravity. We know that organ to be the source of postural reflexes employing the extrinsic eye-muscles. The proprioceptive mechanism of the eyeball muscles is therefore yoked with that of the otic labyrinth in reflex action. Following the principle established in like cases, the inference is that the sense-impressions of the two are likewise associated. This means that the orientation of the retina in space in regard to the line of gravity, that is to say in the mind in regard to verticality, results from co-operation between the special gravity sense-organ and the muscular

sense of the orbital muscles. The so-called primary position of the eyeball is therefore a posture in which the extrinsic ocular muscles cooperate with the otic labyrinth, and the perception of that posture is based on sense-data from both those sources. That posture, however, because it is sensed visually, is perceived by the mind not as a state of the eyeball, but as a state of the external world, of the world as seen; it is "projected."

It appears, so far as space orientation is concerned, as a direct perception of the orientation of the external world. In the observation above the verticality of the line seen by the three retinal points in the primary eye-posture has therefore an otic and an ocular muscle factor combined in it. That a change as regards verticality occurs for those same three retinal points when the eye-posture becomes a secondary oblique one, although the head and therefore the labyrinth posture remains unchanged, shows that in the visual perception of verticality the otic labyrinth datum is so bound up with the proprioceptive datum from the eye-muscles that the latter is a condition for the meaning of the former. Visual local signature as regards the spatial orientation connoted by verticality and deviations therefrom is therefore compounded of at least three factors, namely, retinal, proprioceptive from the extensive eye-muscles, and otic labyrinthism. There is almost certainly a further, though probably minor, factor in it, and that a proprioceptive one, with its source in the muscles of the neck. Recent experiments by de Kleijn (*Archives néerlandaises de Physiologie*, tome ii, p. 644, 1918), show that in the rabbit alterations in the posture of the neck, especially of the two uppermost segments, provoke and maintain definite postures of the eyeballs. These he determined after previous extirpation of the otic labyrinths. They resembled those provocable from the labyrinths themselves, and like those latter were, so to say, in the interest of retaining the retina in the position from which the altered posture of the head displaced it. Sensory impressions of neck-posture have therefore probably to be added to the factors implicated in visual perception of orientation as regards verticality and inclinations thereto.

The above simple observations have been confined to uniocular vision in order to render description and consideration of them more easily given and more clearly followed. But the instances cited, though individual cases only, are of widely applicable type. The upshot of similar binocular observations is similar and similarly explicable. In binocular observations the greater intrusion of the third dimension makes the problem more complex but at the same time enhances its

interest. All, however, that is attempted here is to call attention to some simple yet cogent evidence of an important contribution made by the proprioceptive nerves of the external ocular muscles even to uniretinal space perception. It is not that such contribution is unexpected. On the contrary it is but what on grounds of analogy with other organs, e.g., the hand, we should expect. In so saying, the word "organ" seems preferable to the word "sense." If we state the analogy as one between visual perceptions and other specially endowed perceptions, such as tactual, we run a risk of possibly obscuring what is one of the objects of this short paper to make clear. For what the paper desires to insist upon is that the spatial perceptions under discussion are not purely visual, but are in fact, though such nomenclature would be cumbrous, visuo-musculo-labyrinthine, and their analogy is with tactuo-musculo-labyrinthine.

Finally, apart from subscribing or not subscribing to the general doctrine of psycho-physical parallelism, there is a conviction which the neurologist studying the taxis of the nervous system cannot but derive. If in the sensation or perception which belongs to a particular act analysis reveals components derived from nerves of two or more sensual species, the taxis, even though subconscious, of the muscles employed in that act, whether movement or posture, will likewise involve the co-operation of those same two or more species of afferent nerve. Hence, in the ocular reactions discussed, impairment of the muscular sense of the eye muscles will impair not only the spatial perceptions, but also the taxis, the spatial reaction, even the subconscious and purely reflex taxis, of the eye-movements and eye-postures normally accompanying the perceptions. The proprioceptive afferents of the eye-muscles at their exit from the central nervous system are, unlike the proprioceptive afferents of most muscles, not separated from the motor fibres. This makes a difficulty for the experimental investigation of the influence which their destruction would have upon the movements and postures of the eye. They cannot for experiment be severed apart from the motor fibres themselves. But in tabes we have a disease which attacks systematically the proprioceptive afferents, and spares at least for long the motor fibres. For the problem touched in the present paper it seems significant that squints, often transient in character, are not infrequently an early feature of tabes.

SOME PRINCIPLES OF NEUROLOGY.[1]

BY HENRY HEAD, M.D., F.R.S.

TO-NIGHT we hold the first meeting of this Section after the close of the greatest war in the history of the world. We have scarcely wakened from the long nightmare in which for more than four years we have lived. As with many of its victims, who came under our care, the horror has been so oppressive that the dream still haunts our first waking hours. We of all members of the community have cause to recognize that this victorious peace has been won by the sacrifice of innumerable young lives; and for us older men the future must be dedicated to making the world a better place for those who are to take up our burden.

It was of these young men I was thinking when I meditated the subject of my Presidential Address. For it is exactly twenty-six years since I had the honour of reading my first paper, on "Pain in Visceral Disease," before the Neurological Society. Looking back over a quarter of a century, it seemed to me that I might employ my discourse most profitably by considering certain principles, which underlie the standpoint of neurology to-day. I am not going to weary you with an historical epitome. In this quarter of a century there have been no startling discoveries; but I believe that to-day the outlook of the younger generation is fundamentally different from that in which we were brought up, and I shall attempt to indicate the direction in which it seems to me the science of neurology is moving.

The cataclysmic events of the last four years have shaken men's belief in the old order, and medicine has not escaped the universal demand for a restatement of current values. The young are looking to us to enunciate the principles on which our teaching is founded. They are not disposed to accept without criticism conventional explanations. They regard with scepticism the statements, current in text-books, that the manifestations of an epileptic convulsion are the expression of "irritation of the cortical centres," or that aphasia is explained by

[1] Presidential Address delivered before the Section of Neurology of the Royal Society of Medicine on November 14, 1918.

"the destruction of visual, auditory or motor images." Their curiosity is no longer satisfied by attributing the sensory changes, caused by a peripheral nerve injury, to a "paræsthesia" or "hypo-æsthesia." And indeed words of this order are but anodynes to the conscience. They explain nothing; they serve only to put to sleep the salutary feeling, that further investigation is necessary.

Satisfaction with words, that are in many cases nothing more than a restatement of the problem in bastard Latin and Greek, was one of the most remarkable characteristics of the last quarter of a century. No better example could be found than the misuse of the word toxæmia. We are assured that certain diseases are due to this cause; but, although we know much about the pathological changes in the central nervous system, the symptoms they produce, and the course of the disease, the "toxin" is purely hypothetical. Everywhere we find this remarkable tendency to explain the known by the unknown.

Now every student of natural science should retain something of the simplicity of the child. You all remember the story of the Emperor and his new clothes. Two weavers asserted that they had woven a cloth of extreme beauty and fineness; it had, however, one unusual characteristic. It was invisible to those who were stupid, or unworthy of the post they held. Neither the Emperor nor his courtiers could, it is true, see the stuff, but each was anxious not to betray himself, and all were loud in its praises. Royal robes were made of this wonderful material; but, as the procession wound through the streets, a child called out: "Why he has nothing on," and the child's saying passed from mouth to mouth among the crowd. So the young to-day are calling to us to recognize that many of the terms we use so glibly mean nothing. They do not cover the nakedness of our explanations.

This satisfaction with names is apparent in our conceptions of disease. No better example could be found than the customary attitude of clinicians towards syphilis of the central nervous system. Tabes dorsalis and general paralysis of the insane are thus spoken of as "diseases." In reality, there are two factors only in the morbid manifestations produced by syphilis of the nervous system, the character of the infective activity and the site of its anatomical incidence. The *Spirochæta pallida* may attack almost any structure, and the "disease" expresses the functions of the tissues affected. Tabes dorsalis is a convenient term to express the fact, that the principal focus of the destructive process lies in the posterior columns, and "general paralysis" simply indicates that it has fallen mainly on the higher cerebral centres.

Year by year the line, once so firmly drawn between tabes dorsalis and dementia paralytica, grew fainter as the identity of the pathological process underlying the two conditions was recognized. With the invention of the term "tabo-paresis," the boundaries between the two diseases fell. We now know that any nervous function, from the lowest reflexes to the highest intellectual activities, may be disturbed in consequence of syphilitic infection of the nervous system; and it is only by arbitrary selection that these diverse signs and symptoms can be erected into "diseases." Then again "parasyphilis" was supposed to be the manifestation of a process, syphilitic in origin, but not strictly syphilitic in nature. We now believe that "parasyphilis" is nothing more than an anaphylactic reaction in the tissues of the central nervous system, which have been rendered hypersensitive in accordance with their peculiar lymphatic supply. "Parasyphilis" does not differ from "chronic cerebral syphilis" in any essential pathological particular. It is merely a similar reaction in a different tissue. No better example could be given of the law that, in morbid conditions of the nervous system, the form assumed by the disease is determined by the site of the destruction, whilst the course it runs is dependent on the natural history of the pathological process.

During the last few years the attitude of the neurologist has undergone a subtle change, not only to disease, but also to its general effect upon the patient. At one time everyone was seeking for a sign or a syndrome. Happy the man who could discover a new reflex; it did not matter that he left it unexplained, and failed to correlate it with other ancillary functions. It was a "fact," and to it his name was attached.

But the discovery of such a phenomenon is nothing more than the statement of the terms of the problem awaiting solution. To find its explanation we must look to the behaviour of the nervous system as a whole, and observe how its reactions are changed. In many cases, this leads to the consideration of phenomena, which would have been thought frivolous by the older generation. Take, for example, the importance attached to the patient's account of his own sensations, or the diagnostic value now attributed to certain dreams.

In 1901, I described certain mental changes, associated with disease of the heart and lungs, and showed that they formed another aspect of referred visceral pain. This work fell dead; for those who were interested in morbid conditions of the internal organs cared nothing for changes in the mental state of the patient; on the other hand the

alienists denied the facts, because of the remoteness of Asylum life from the conditions of Hospital experience. They made no effort to discover, whether such remarkable examples of the dependence of mental states on disturbances of bodily functions were really open to their investigation. To-day, however, this work is falling into its place as a small contribution to the relation of body and mind.

Interest in the functions of the nervous system, as revealed by disease, is steadily growing. The English school has always been essentially physiological, from the days of Marshall Hall onwards; but this growing attention to function is mainly due to the teaching of Hughlings Jackson. He sprang from the physiologists of the middle of the last century, and was deeply imbued with the principle of evolution, not only of structure, but of function. But his contemporaries became increasingly obsessed with the study of anatomical and topographical details. As years passed by, the teaching of the day moved away from Jackson's conception of an evolution of function, still demonstrable in the activities of the nervous system. Finally his doctrines were scarcely comprehensible to those of us who were brought into daily contact with him in the wards, seduced as we were by the glib generalities of more popular teachers. But, when we came to think for ourselves, we found that his conception of a functional hierarchy, in which one form of activity was dominated by another, standing higher in the evolutionary scale, explained much that was otherwise inexplicable in the phenomena of nervous disease. This swing back to the physiological aspect was quickened by the exquisite researches of Sherrington, and the issue of his "Integrative Action of the Nervous System," in 1906, marks an epoch in the progress of neurology.

We then began to appreciate, that the existence of the central nervous system was due to the necessity of producing coherent action in a plurisegmental organism. Out of the primitive materials at her disposal, Nature was forced to develop a mechanism capable of integrating the physiological forces evoked by relations with the external world. As the animal rose in the evolutionary scale, the functions required of the nervous system became more and more complex, and out of the anatomical structures of a lower organism had to be developed a machinery capable of exercising these higher activities.

This was only possible by integrating the crude physiological processes excited by external stimulation, or arising in response to the action of internal forces. A prick excites a universal tendency to withdraw the part exposed to stimulation; it can also evoke a highly

organized movement, such as the scratch-reflex, capable of removing the noxious object.

But such reflexes are preordained and admit of no choice. It became necessary, therefore, to develop a controlling mechanism that would permit the animal, either to attack the stimulus locally, or to evade its action by flight. Finally, with the development of the neopallium was given the power of voluntary choice; the reaction was no longer unconscious, but could be preceded by a definite act of discrimination.

This adaptation to a clearly determined end demands a multitude of adjustments, and such integration is the business of the central nervous system. It can only be carried out by utilizing, in a modified form, functions originally developed for a somewhat different purpose. Thus, the withdrawal movement, which forms the basic reaction to pricking the sole of the foot, is controlled by higher centres in the mid-brain and forms the flexor aspect of the stepping reflex. But, when this higher influence is removed, at any rate for a time, as for example by total transection of the spinal cord, the lower reflex becomes manifested in its primitive form as a pure movement of withdrawal, accompanied by evacuation of the bladder and rectum.

Structure is anchored in the past and may express, in its anatomical arrangements, functions which have been transmuted. Many of them have been carried up to centres of more recent origin, whilst others are exercised normally, in a refined form, under the control of those higher in the evolutionary scale. But nothing remains in its old form, unless it is of utility to the organism under some possible conjunction of circumstances.

Thus the afferent impulses from the viscera do not normally enter consciousness. The eupeptic knows nothing of the processes of digestion, beyond a certain gentle sense of well-being. But, under abnormal conditions, afferent impressions from the internal organs are capable of arousing pain and discomfort. When this occurs, one form of this sensory disturbance is referred to the superficial structures of the body and is associated with areas of tenderness, corresponding to a segmental arrangement of the central nervous system. This is not a "hyperæsthesia," but a tendency to react more violently to any stimulus capable of evoking discomfort. The threshold is not materially lowered, but the vehemence of the response is greatly increased.

Now this over-reaction is associated with reflexes, which still reveal their old defensive character. As an answer to visceral pain, the

abdominal muscles become tonically contracted, and the leg is drawn up on the affected side. The sufferer is forced to creep into some sheltered place, and to lie curled up, till he either dies or recovers. All capacity to move as a whole is abolished; the reactions of the part affected now dominate the activity of the complete animal. Visceral reflexes, of this order, are antagonistic to general movements, and this is expressed, not only in muscular immobility, but in the mental attitude which accompanies visceral pain.

Pain is the oldest defensive reaction, and potentially painful stimuli are the basis of all primitive reflexes. It is therefore of importance for higher development, that these impulses should be rendered less effective in favour of those impressions which lead to a more general and discriminative response. But, although they are controlled and even abolished, the mechanism underlying the production of pain must remain in full physiological activity, ready to play its part should occasion arise, in the defence of the body against noxious influences.

The functions of the central nervous system are not a palimpsest, where a new text is written over an earlier manuscript, partly erased. The more primitive activities have been profoundly modified by the advent of the new centres, which utilize some of the faculties originally possessed by the older mechanism. In many cases the higher function could not be exercised, without the existence of these lower powers which it dominates and controls.

When, however, the higher mechanism is thrown out of action the functions of the lower centres are free to exhibit their activity unchecked. Jackson insisted that the manifestations, due to a lesion of the central nervous system, must be considered from a negative and a positive aspect. Injury to the pyramidal system was shown, negatively, in the loss of the finer voluntary movements; but the activity of the lower centres, released from control, was evident in the spastic rigidity of the paralysed parts. In the same way, removal of the control, normally exercised by the cortex over the activity of the optic thalamus, leads to the remarkable condition known as thalamic over-reaction; all stimuli capable of evoking discomfort, and in some cases even pleasurable excitation, cause an exaggerated response on the affected half of the body. This is not due to "irritation"; it is due to release. It is the direct consequence of loss of that control normally exercised by the cortex over the activities of the optic thalamus. Once this control is removed by disease, the lower centre reacts unchecked to any stimulus capable of exciting a response.

It has been the custom to call upon a hypothetical "irritation" to explain all such positive manifestations of nervous energy. The violent flexor spasms and the outbursts of excessive sweating, which occur when the spinal cord is injured, have been attributed to this cause. In reality, they are the expression of a diffuse and massive response to stimuli, applied to parts below the level of the lesion; they are manifestations of a primitive mode of reaction, due to removal of control from above. Involuntary movements in hemiplegia, automatic acts following an epileptic attack, the emotional utterances in aphasia, are all examples of the same phenomenon. The condition of sensibility, during the protopathic stage of recovery from a peripheral nerve lesion, is another instance of a primitive mode of reaction, released from control by the tardy restoration of the epicritic mechanism. Normally the massive "all or nothing" response of the more primitive system is held in check by the localized and discriminative sensations, due to excitation of the epicritic end-organs. But, when the one set of afferent impulses is permitted to play on the ultimate sensory centres unchecked by those arising in the higher mechanism, the response becomes massive and diffuse, and extensity becomes of greater import than intensity.

Had we applied Jackson's law, that the functions of the nervous system are integrated on evolutionary principles, neurology would not have made so many excursions into the wilderness. He taught us that a lesion of the cerebral cortex caused disorder of movement, not paralysis of the muscles. This lesson, however, was not applied to the other functions of the cortex. Much time was wasted on topographical localization of various sensory centres, before the nature had been determined of the functions exercised by the cortex. Now we know that, as far as somatic sensibility is concerned, the cortex is responsible for the appreciation of spacial relations, for the power of responding to different intensities of stimulation, and for the capacity to recognize similarity and difference in external objects, brought into contact with the body. The cortical centres are not concerned with the crude appreciation of touch, pain, heat and cold.

Such principles are not only of theoretical importance; they are perpetually thrust before the neurologist in his daily work. Clinical diagnosis is a by-product of scientific investigation. It is impossible to expose every patient to laborious scientific examination, nor would it serve any useful purpose to do so; but the simple tests, employed in the wards, are valueless until they have been calibrated by more elaborate

investigations. The man who says he can obtain all the information he wants, in cases of injury to peripheral nerves, by means of a pin and a piece of cotton wool, depends on someone else to teach him the significance of these empirical tests. They have no scientific value, until the data they yield are correlated with results, reached by methods capable of measurement.

The charm of neurology, above all other branches of practical medicine, lies in the way it forces us into daily contact with principles. A knowledge of the structure and functions of the nervous system is necessary to explain the simplest phenomena of disease, and this can be only attained by thinking scientifically.

Let us then consider some of the leading principles, which the candidate of the future must master in the course of his initiation:—

(1) When any level[1] of activity is attacked, the most complex functions, and those which have appeared most recently, are the first to suffer; they are also disturbed to a greater degree, and to a wider extent, than those which are simpler or more inevitable in their expression.

An excellent example of this rule is seen in the effect of a lesion of the sensory cortex on the appreciation of the spacial aspects of an external stimulus. Tests, which demand recognition of movement in three dimensions, are more gravely affected than such a comparatively simple one as localizing the position of the stimulated spot; for, with the precautions we habitually adopt, this is an exploration in one-dimensional space. Division of the spacial aspects of sensation according to one, two and three dimensions is obviously arbitrary; but the tests we apply become more or less complex and difficult according as they demand recognition of relations in space of three, two or one dimensions. Consequently, the records obtained by measuring the extent of passive movement, which can be appreciated in the affected limb, are more gravely and extensively affected than those yielded by our method of testing localization.

(2) The negative manifestations of a lesion appear in terms of the affected level.

Thus, if those parts of the cortex are injured which are associated

[1] The word "level" is employed throughout in a strictly functional sense. Any one anatomical organ of the central nervous system may exercise functions of more than one physiological level. Thus the optic thalamus contains, not only the termination of the fillet, but also the centre for the affective aspects of sensation. For the same reason, a lesion of the post-central cortex not only produces loss of certain sensory faculties, but may also cause hypotonia in the affected parts of the body.

with speech, the consequences are not an affection of some totally different function, such as visual or auditory images, but are shown in terms of defective speech. The business of a clock is to show the time. Faulty action of the main-spring may cause it to go fast, to go slow, or to stop. But we cannot look at the face of the clock and say "That is strong main-spring time"; all we can say is that the clock is fast. So the negative manifestations of a cortical lesion affecting speech are presented to us in the form of a disturbance of speech, not as a destruction of images.

In the same way, morbid conditions at the reflex level appear as changes in the reflexes; a disturbance of cerebellar activities is seen in inco-ordinate movement; whilst an injury to the sensory cortex affects the discriminative aspects of sensation, a purely mental function.

(3) A negative lesion produces positive effects by releasing activities, normally held under control by the functions of the affected level.

I have already given many illustrations of this law. The phenomena of the mass-reflex after injury to the spinal cord and of spastic rigidity in hemiplegia are examples on the motor side; protopathic sensibility and thalamic over-reaction illustrate similar conditions amongst afferent activities.

(4) The functions of the central nervous system have been slowly evolved by a continuous process of development. The methods, by which this gradual progress from lower to higher efficiency has been reached, are still manifest in the phenomena of its normal activity.

Thus the lowest reflexes give the most definite response; there is little or no choice, the answer is inevitable. They are, as Jackson expressed it, "highly organized." But further development of the needs of the animal demanded a reaction that was less fixed; some variation must be permitted. This led finally to the domination of many reflex manifestations by consciousness. What at lower levels appeared a variable response, became, with the progress of evolution, voluntary control.

(5) Integration of function within the nervous system is based on a struggle for expression between many potentially different physiological activities.

Let us consider the following example, drawn from the afferent side. A metal test-tube, containing water at 45° C., normally evokes a sensation of pleasant heat. But it is easy to show that this temperature, suitably applied, stimulates the cold-spots and then appears to be cold.

If, by chance, both the end-organs for the reception of heat and cold are absent, pain is produced. Thus the same temperature is capable of exciting heat, cold and pain; and yet under normal circumstances it evokes a sensation of pleasant warmth. Evidently, the incompatible impulses, due to stimulation of the cold- and pain-spots, are prevented from reaching consciousness.

Such integration occurs at several stages, during the passage of afferent impressions through the central nervous system. Those, alike in their qualitative potentialities, are gathered together, whatever may have been their origin, at the periphery. Thus all impulses capable of arousing pain come together in the spinal cord. In the same way, there are separable paths for those associated with sensations of heat and cold. Finally, on higher physiological levels is fought out the struggle for final dominance, and, of the warring impulses, one group only excites a conscious response.

The processes by which this integration is rendered possible are three in number. First of all those impulses, potentially of a like sensory quality, are gathered together. Secondly, all impulses capable of exciting sensations of a different quality are rejected by the receptors, which guard each functional level. The third method is manifested in the phenomena of adaptation. Water at 30° C. may appear under suitable external conditions to be neither hot nor cold. But, when the hand has been previously soaked in water at 45° C. for some time, a temperature of 30° C. will seem to be cold. Conversely adaptation to water at 15° C. converts 30° C. into a warm stimulus. This power of adaptation to the conditions of the environment, and consequent shifting of the neutral point is one of the most important factors in the mechanics of integration. No stimulus acting over a long period can remain continuously at the same level of efficiency; it leads to a state increasingly favourable to the appearance of the opposite phase of activity. This is the essential condition underlying the tendency to biphasic reaction so characteristic of the central nervous system.

These three processes, acceptance by similarity, rejection by difference, and biphasic dispositions, form the main features of the physiological functions of the central nervous system. They are factors which lead to integration, whether we are dealing with reflexes or with such psychical acts as sensations.

They are interposed between the vital consequences, produced by the impact of a physical stimulus on peripheral end-organs, and the final processes of consciousness. We have no right to speak of psycho-

physical parallelism; we ought rather to consider on the one hand physiologico-physical responses and on the other psycho-physiological relations.

Thus, between the impact of a physical stimulus on the surface of the body and the movement or sensation it evokes, lie the innumerable reactions of the physiological level. Here the form assumed by the conscious response is prepared to a degree scarcely suspected until recently. Many of the impressions produced by a single external stimulus are incompatible with one another, and some of them must give way in the conflict. But the result of the struggle is not fixed or pre-ordained; it may be reversed by some previous occurrence, which has changed the disposition of the central nervous system. The form assumed by a reflex may be determined by the character of the movement which preceded it, and the phenomena of sensory adaptation depend upon the active influence of the past in present events.

Moreover, the general resistance of the central nervous system to certain impulses varies greatly at different times and in different persons. This is particularly evident in the case of pain. We are all subjected to innumerable painful impressions, which under normal conditions never reach consciousness; but if the resistance, either local or general, is lowered, these impulses may underlie definite sensations of pain.

We neurologists are brought into daily contact with these diverse functional reactions and can watch the processes of evolution, visible in the actual behaviour of the central nervous system. We work in the passage-way between the physical universe and the dwelling-place of the mind. We see the coming and the going, and we alone can record which of the many aspirants has conquered the right to enter or to leave that council chamber of human activities.

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